Dystonia in complex regional pain syndrome: clinical, pathophysiological and therapeutic aspects
Rijn, M.A. van

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Cerebral Activation during Motor Imagery in Complex Regional Pain Syndrome with Dystonia

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Abstract

**Background:** The pathogenesis of dystonia in Complex Regional Pain Syndrome (CRPS) is unclear. In primary dystonia, functional magnetic resonance imaging (fMRI) has revealed changes in cerebral networks during execution of movement.

**Objectives:** To determine cerebral network function in CRPS patients with dystonic postures.

**Design:** Assessment of cerebral processing related to both execution and imagining of hand movements with fMRI in patients and controls.

**Subjects:** 8 CRPS patients with dystonic postures of the right upper extremity and 17 age matched healthy controls.

**Results:** Compared with controls, imaginary movement of the affected hand in patients showed reduced activation ipsilaterally in the premotor and adjacent prefrontal cortex, and in a cluster comprising frontal operculum, the anterior part of the insular cortex and the superior temporal gyrus. Contralaterally, reduced activation was seen in the inferior parietal and adjacent primary sensory cortex. There were no differences between patients and controls when they executed movements, nor when they imagined moving their unaffected hand.

**Conclusions:** The altered cerebral activation pattern in patients with CRPS linked dystonia most likely reflects an interface between pain-associated circuitry and higher order motor control, which points at a specific mechanistic pathophysiology of this type of dystonia.
Introduction

Complex Regional Pain Syndrome type 1 (CRPS), also called Reflex Sympathetic Dystrophy (RSD), is a syndrome predominantly characterised by a variety of sensory, autonomic and trophic features. Symptoms include pain, oedema, hyperhydrosis and impaired function. Growing evidence indicates that CRPS may also include some form of movement disorder, like tremor and dystonia.

Dystonia is characterised by involuntary sustained muscle contractions, causing twisting and repetitive movements or abnormal postures. Functional brain imaging with PET and fMRI has provided valuable new insights in the role of altered activation of basal ganglia-cortical networks during execution of movement in focal and generalized dystonia. Underactivation of the primary motor cortex and overactivation of the somatosensory cortex, prefrontal -, premotor - and parietal cortical regions have been reported. Other studies showed an overactivation of the primary motor cortex and underactivation of the premotor cortex. These inconsistencies may result from a combination of differences in scanning procedures, tasks and a varying degree of dystonia during motor execution. However, a distinct pathophysiology underlying different forms of dystonia may equally be an option.

The pathophysiology of CRPS itself remains a controversial issue. Some features of CRPS favour a spinal aetiology, other indicate a cerebral reorganization in both the sensory and motor domain. A recent fMRI study in CRPS, focusing on mechanical hyperalgesia, reported alterations in nociceptive, cognitive and motor processing. Hitherto, no functional imaging study in dystonia of CRPS during movement execution has been performed.

In overt dystonic movement, altered sensory feedback (in particular noxious input) during painful movements is a potential confounder in functional brain imaging, which can be reduced by motor imagery, i.e. mental rehearsal of a motor act without overt movement. Previous work suggests that the volume of brain activation differs between execution and motor imagery, but the distribution of cerebral activity tends to be partly similar. Motor imagery is used in sport to improve performance. A positive effect of motor imagery in the rehabilitation of CRPS patients has been established.

In this study we aimed to explore the distribution of cerebral activations in CRPS patients with tonic dystonia during both motor execution and imagining of movement, of affected as well as unaffected limbs. Based on the clinical resemblance with other forms of dystonia, we hypothesised to find a functional alteration in regions supporting a primary motor function, and in circuitry associated with higher-order motor control, particularly in the parietal cortex.
Subjects and methods

Subjects
Eight patients (seven female, mean age 46.4, SD 6.0 years) with CRPS related dystonia from the Leiden University Medical Center and seventeen healthy volunteers (15 female, age 42.9, SD 9.2 years), matched for age, were studied. All patients fulfilled the officially accepted diagnostic criteria for CRPS of the IASP. Revisions of these diagnostic criteria are under consideration. Furthermore, the presence of tonic dystonia in at least the right upper extremity was obligatory. The presence of dystonia in the CRPS-affected limb was based on the presence of prolonged muscle contractions resulting in abnormal postures or movements of the limb. In upper limb dystonia such involuntary muscle contractions resulted in typical flexion postures of the hand and fingers. In all patients a tonic stretch reflex was present. Passive stretching of the affected digits induced increased flexor activity. The dystonic limb was also always the CRPS affected limb. In five patients the right leg was also affected, in one the left leg and in one both legs (Table 1). Patients in which the left arm was affected by CRPS were excluded. Right handedness was obligatory and was assessed according to the Dutch Handedness Questionnaire. The ability to perform mental imagery was assessed by the Vividness of Movement Imagery Questionnaire (VMIQ). Further assessments included a neurological examination. The T1 weighted MRI scan did not show pathology. Informed written consent was obtained and the study was approved by the Medical Ethical Committees of the Groningen and Leiden University Medical Centers.

Tasks
Subjects performed four tasks: execution and imagination of flexion/extension movements of the separate right and left wrist. The movements were performed in a vertical plane and paced at 0.5 Hz by a visual stimulus: in response to each stimulus one self-paced extension-flexion cycle was made. The forearms were positioned in pronation on pillows. All tasks were preceded by a rest condition. All conditions had a duration of 30 seconds. Three runs were performed lasting 12 minutes each. In each run, 12 response blocks were scheduled. For each subject, tasks were presented in a random, but balanced order. Subjects were monitored and videotaped during scanning. Special attention was paid to voluntary and involuntary movements of wrists. Prior to the experiment, subjects practised the tasks outside the MRI scanner. They were instructed to imagine moving their wrist freely. Their limbs were not within their field of view. After data acquisition all patients reported pain during the movement execution task. None of the patients reported pain during the imagined movements. Pain was not formally quantified by standardized questionnaires.
Cerebral Activation during Motor Imagery in Complex Regional Pain Syndrome with Dystonia

Functional imaging
Subjects were scanned using a 3 Tesla Philips MRI scanner (Best, the Netherlands). The following pulse sequence parameters were used: single shot EPI; 46 slices; 3.5 mm slice thickness; no gap; 224 x 224 mm field of view; 64 x 64 scan matrix; transverse slice orientation; repetition time 3000 ms; echo time 35 ms; flip angle 90°. Three runs of 240 brain volumes each were acquired, i.e. 10 volumes per 30 seconds condition block. In addition, a T1-weighted whole brain anatomical image was acquired (resolution 1x1x1 mm).

Statistical analysis
Spatial pre-processing and statistical analysis (random effects) was carried out using Statistical Parametric Mapping (version SPM2). The functional images were realigned, normalised and subsequently smoothed with an isotropic Gaussian filter using an 8 mm Full Width-Half Maximum Gaussian kernel. Head movements were more frequently seen in the patient group. This reflects the difficulties the patients had in performing the tasks. Optionally, the estimated head-motion parameters were used as covariates as described by Friston et al. Only minor differences were encountered in this comparison, indicating the presence of task-related head movements. However, areas affected by motion did not show overlap with areas activated during the tasks, demonstrating that the group result was not caused by head motion. Note, for the reported results motion correction has been applied. In the first analysis, the movement and imagining conditions of each hand were compared with rest for each single subject (first level analysis). For within-group analysis, for the patient and control group respectively, these contrasts were tested using a one sample T-test (second level analysis). For the larger control group (17 subjects), a high threshold at voxel level was used ($P < 0.05$ Family-wise Error (FWE); extent threshold ≥ 5 voxels). This avoided overlap of activations which would have blurred regional identification when thresholded at $P < 0.001$ (uncorrected). For patients (8 subjects) a threshold at $P < 0.001$ (uncorrected) was used. This was done as to look for the spatial distribution of a circuitry with general resemblance to that observed in controls. For a between-group analysis (i.e. patients compared to controls) a two-sample T-test was used ($P < 0.001$ (uncorrected)). Resulting clusters for both tests were considered significant at $P < 0.05$ (cluster-level corrected for whole brain volume).
Results

Findings on the VMIQ questionnaire (patients 110 ± 52, control subjects 83 ± 34; two-sample T-test, 2-tailed $P=0.133$) revealed no significant differences.

In both controls and patients, activated areas during imagining showed a symmetrical distribution and activation of the sensorimotor cortex was not observed. Activation in the patient group appeared to be less robust than in the controls for the four different tasks (Figure 1, Table 2). By visual inspection, it already was apparent that the patients’ activation networks were most affected during imagining of motor performance with the affected hand. But direct comparison of the figures only allows observation of a trend, partly because of differences in population size (17 controls versus 8 patients). The statistical significance of differences between the two groups can only be established by formal between-group analysis. Such statistically significant differences between patients and controls were only obtained during imagining right hand movements. No statistically significant between-group differences were obtained for the three other tasks.

During imagining of right hand movements three regions were significantly less activated in patients compared with controls. No increases were seen in the patients during this task. These foci of reduced activation were distributed ipsilateral over both the middle frontal gyrus, comprising the prefrontal cortex and premotor cortex ($P$ corrected-cluster-level 0.030, cluster size 186 voxels), and the anterior part of the insular cortex adjoining the superior temporal gyrus and the inferior frontal gyrus ($P$ corrected-cluster-level 0.010, cluster size 242 voxels). In the hemisphere contralateral to the imaginary moving hand, the postcentral gyrus and inferior parietal cortex were less activated in the patient group ($P$ corrected-cluster-level 0.030, cluster size 186 voxels), (Figure 2, Table 3).
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at scan</th>
<th>Sex</th>
<th>Preceding trauma</th>
<th>Disease duration in years</th>
<th>Affected body part</th>
<th>Dystonic posture</th>
<th>Sensory modalities</th>
<th>VMIQ</th>
<th>Movement during tasks</th>
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<td>1</td>
<td>44</td>
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<td>fist right hand, inversion/ flexion left foot</td>
<td>decreased touch and vibration in affected body parts, hyperpathia right arm; stereognosis intact</td>
<td>122</td>
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<td>48</td>
<td>f</td>
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<td>8</td>
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<td>1990 thrombosis right arm*, no trauma°</td>
<td>11*, 10°</td>
<td>right hand*, right leg°</td>
<td>extension dig 1; flexion PIP and DIP dig 2,5; extension MCP, flexion PIP and DIP dig 3,4; flexion elbow right arm; flexion toe</td>
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Table 1. continued

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<td>operation$^<em>$, local fracture$^</em>$</td>
<td>11$, 9^*, 7^\circ$</td>
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$^*$low frequency = $1/3 - 1/5$ Hz
Table 2. Areas activated during motor execution and imagining in controls and patients, compared with rest

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Activations at $P$ corrected on cluster-level of $< 0.05$ were considered significant, which is indicated by the + sign.

“Contra” denotes activation in the hemisphere contralateral to the performing limb, “ipsi” denotes activation in the hemisphere ipsilateral to the performing limb.

¹ Initial response height thresholded at voxel-level FWE $< 0.05$, extent threshold $\geq 5$ voxels.

² Initial response height thresholded at voxel-level $P$ uncorrected $< 0.001$, extent threshold $\geq 5$ voxels.
Figure 1. Areas of activation in controls (n=17) and patients (n=8)

Four different tasks compared with rest condition, projected on a template rendered brain image.
$P$ uncorrected $< 0.01$, extent threshold $\geq 5$ voxels.
Table 3. Areas significantly less activated in patients than in controls during imagining of right hand movements

<table>
<thead>
<tr>
<th>Brain region (Brodmann Area)</th>
<th>Stereotactic coordinates</th>
<th>Contralateral (left)</th>
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<tr>
<td></td>
<td>Ipsilateral (right)</td>
<td>z</td>
</tr>
<tr>
<td></td>
<td>x</td>
<td>y</td>
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<tr>
<td>Premotor cluster</td>
<td>Middle frontal gyrus (BA 8,9)</td>
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<td></td>
<td>Premotor cortex (BA 6)</td>
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<tr>
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<td>Insular cortex (BA 13)</td>
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<td>Superior temporal gyrus (BA 22)</td>
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<tr>
<td>Anterior parietal cortex</td>
<td>Postcentral gyrus (BA 2)</td>
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<td></td>
<td>Inferior parietal cortex (BA 40)</td>
<td>-34</td>
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</table>

Anatomical regions, Brodmann areas and coordinates (according to the Montreal Neurological Institute) of activated clusters. Initial response height thresholded at voxel-level $P$ uncorrected $< 0.001$, extent threshold $\geq 5$ voxels. Activations at $P$ corrected on cluster-level of $< 0.05$ were considered significant. Positive $x, y, z$ coordinates indicate locations respectively right, anterior and superior of the middle anterior commissure.
Figure 2. Areas with reduced activation in patients compared with controls during imagining of movement of the right hand.

Areas projected on glass brain and transversal slices of a mean template image. $P < 0.05$ (volume corrected, cluster-level). (1) Ipsilateral middle frontal gyrus and premotor cortex, (2) ipsilateral anterior part of insular cortex, superior temporal gyrus and inferior frontal gyrus, (3) contralateral inferior parietal cortex and postcentral gyrus.

Discussion

Both execution and imagining of the motor task in our healthy volunteers results in activation of previously described cerebral circuitry\textsuperscript{14,15,24}. In CRPS patients, however, the motor imagining paradigm revealed a conspicuously reduced activation of cortical networks that subserve imagining of movement of the affected limb, in comparison with controls. Only two other imaging studies have reported an imagining paradigm in dystonia patients. In a preliminary PET study idiopathic torsion dystonia patients showed a similar activation pattern as controls\textsuperscript{25}. In a recent fMRI study on post-stroke dystonia, mental representations of movement of the affected hand resulted in overactivity of the ipsilateral inferior parietal cortex, insula, bilateral prefrontal cortex and other cortical areas\textsuperscript{26}. Part of these regions are also involved in our CRPS patients, although we found underactivity. This difference may be due to differences in the underlying pathophysiology or the application of different scanning paradigms.
Imagining of Movement

All patients recalled the ability to perform the imagining task with their affected limb. Moreover, the ability of patients for imagining movement in general did not significantly differ from the controls, as we inferred from the VMQI questionnaire. This demonstrated the ability of the patients to perform a movement imagery task, although we have no behavioural characteristics to answer the question to what extent imagining movement of the affected hand was correct. In CRPS (without dystonia), prolonged time for imagining moving the affected body part, when compared to the not-affected body part, has previously been explained by a distorted cortical correlate of the body scheme. Such a distorted body image has also been inferred from referred sensations, mislocalization of tactile stimulation and the experience of an increased size of the affected limb.

The aforementioned behavioural findings are consistent with the idea that cortical reorganization plays an important role in CRPS. We think it likely that changes in body scheme, associated with changes in cortical representation, play an important role in our results. By using sensory stimuli, cerebral reorganization in CRPS has also been demonstrated to occur in the nociceptive (or sensory) domain as well as in cognitive and motor domains. A recently published case-report even mentioned a temporarily increase in pain and swelling of the affected hand in a CRPS-patient after imagined movements. Although this was not mentioned by our patients and the report was limited to one patient, it implies that symptoms of CRPS may be mediated by cortical mechanisms associated with (imagined) movement of the affected body part.

In order to comprehend the specific distribution of the regional decreases in our movement execution and movement imagining study, it is important to consider how the functions of these regions may provide a logical combination in the context of pain and disturbed motor control. The premotor cortex is related to planning and organization of movement. Both impaired activation and enhanced activation in the premotor cortex during a motor task in different forms of dystonia has been reported. The inferior parietal cortex is an association area, which receives information of different sensory modalities and thus holds a strategic position in processing space perception, body scheme and so in linking sensation to motor control. The posterior part of the sensory cortex which constituted the anterior border of the parietal activation in our group is particularly involved in the proprioceptic sensation related to limb movement.

The posterior insula is known as a secondary motor area. For the anterior part of the insula, however, a relation with motor control is less obvious. The latter has a dominant role in autonomic regulation. The paralimbic cortex in the anterior superior temporal sulcus, along with anterior insula and orbitofrontal cortex, have been proposed to pro-
vide an interface between limbic cortex in the medial temporal lobes and frontoparietal association cortices. The anterior part of the insula and superior temporal sulcus are situated between the posterior cortex and frontal cortices, thus linking multimodal perception of stimuli and executive processes. The anterior insula is involved in pathways that are critical for mental processing of pain-related experiences in patients with an amputated hand during imagining of painful finger movements and in a pin-prick hyperalgesia study in CRPS patients.

In view of the long disease duration (mean 11 years) of our patients, long-lasting pain may have induced changes on efficient motor control, reflected by a decreased activation in circuitry providing limbic access to higher-order motor control.

**Execution of Movement**

Motor execution of the affected side in patients showed only non-significant differences between patients and controls. At first sight, this may look strange. On the other hand, the between-group comparison may not have reached statistical significance as a consequence of higher intersubject variability in the activated areas during execution. Such variability may be caused by differences in effort to move. Our most plausible explanation is the altered sensory feedback in the patients, as they experience pain when performing the movement task. This sensory feedback may result in activation of cortical areas, scaling down the areas activated in relation with the execution of movement. However, the fact that we did not find a consistently increased activation in pain-associated circuitry makes us reluctant to provide a definitive explanation in this matter. Findings on motor execution in our patients with dystonia of CRPS, are different from those found in other causes of dystonia, although studies on dystonia, in general, have reported contradictory findings. This can often be attributed to methodological differences, but a different pathophysiology for different forms of dystonia may also be an option. In the case of CRPS, a different pathophysiology of dystonia is likely.

In conclusion, patients with CRPS and dystonia displayed areas with decreased activation during imagining tasks that are involved in planning of movement, multimodal sensorimotor integration, autonomic function and pain. Pain may profoundly alter the cerebral organization of movement by functional interaction between these regions.

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