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Altered Resting-State Functional Connectivity in Complex Regional Pain Syndrome

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Abstract: This study explored the functional connectivity between brain regions implicated in the default mode network, the sensorimotor cortex (S1/M1), and the intraparietal sulcus (IPS/MIP) at rest in patients with complex regional pain syndrome. It also investigated how possible alterations are associated with neuropathic pain. Our group used functional magnetic resonance imaging to investigate functional brain connectivity in 12 complex regional pain syndrome patients in comparison with that in 12 age- and sex-matched healthy controls. Data were analyzed using a seed voxel correlation analysis and an independent component analysis. An analysis of covariance was employed to relate alterations in functional connectivity with clinical symptoms. We found significantly greater reductions in functional default mode network connectivity in patients compared to controls. The functional connectivity maps of S1/M1 and IPS/MIP in patients revealed greater and more diffuse connectivity with other brain regions, mainly with the cingulate cortex, precuneus, thalamus, and prefrontal cortex. In contrast, controls showed greater intraregional connectivity within S1/M1 and IPS/MIP. Furthermore, there was a trend for correlation between alterations in functional connectivity and intensity of neuropathic pain. In our findings, patients with complex regional pain syndrome have substantial spatial alterations in the functional connectivity between brain regions implicated in the resting-state default mode network, S1/M1, and IPS/MIP; these alterations show a trend of correlation with neuropathic pain intensity.

***Perspective:** This article presents spatial alterations in the functional resting-state connectivity of complex regional pain syndrome patients. Our results add further insight into the disease states of CRPS and into the functional architecture of the resting state brains of pain patients in general.*

***Key words:** Complex regional pain syndrome, resting state, functional magnetic resonance imaging, default mode network, sensorimotor cortex.*

Complex regional pain syndrome (CRPS) is a painful disorder. It may develop in about 5% of all upper or lower limb trauma or nerve lesions.[24] The clinical presentation of CRPS consists of a relatively characteristic triad of dysfunction in the autonomic (edema; sweating abnormalities; alterations in skin color, skin temperature, and hair and nail growth), sensory (hyper- or hypoalgesia, pain, allodynia), and motor (paresis, tremor, dystonia) systems.[24] Neglect-like symptoms have also been reported.[11,13] Besides clinical symptoms, CRPS is associated with a significant reduction in quality of life and capability.[4] The pathophysiology of CRPS comprises distinct alterations in the peripheral, autonomic, and central nervous systems.[26] Previous functional imaging studies in patients with CRPS affecting the hand showed substantial somatotopic changes in the primary and secondary somatosensory cortices (S1, S2) contralateral to the side with the CRPS symptoms.[19,22,30] Magnetoencephalography demonstrated that the cortical hand representation for the side affected with CRPS was significantly shrunken. Additionally, the hand position was shifted toward the lip. A predictor of the somatotopic reorganization was spontaneous pain, especially mechanical hyperalgesia.[22,23] Somatotopic changes

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were also found in the motor and supplementary motor cortices and in the intraparietal sulcus (IPS).[20] In recent years, neuroimaging studies have focused on the functional interplay between certain brain regions at rest, the so-called resting state networks. Resting state networks consist of highly correlated organized brain areas in the low-frequency range (<.1 Hz) of the blood oxygen level–dependent signal.[10,33] The default mode network (DMN) is one of several RSNs and is the most thoroughly investigated and stable network, which is suspended during various cognitive tasks.[10] It is characterized by balanced positive and negative correlations between activities in the dorsal and ventral medial prefrontal cortex (MPFC), the medial parietal cortex (posterior cingulate cortex [PCC], precuneus [preCUN]), and the inferior parietal cortex.[5,10,34] The components of the DMN correlate with behavioral performances and emotional measures and are involved in self-referential processes such as introspection, self-monitoring, autobiographic memory, comprehension of emotional states, intentions of others, and planning for the future.[2,5,29,33] Interestingly, pain seems to affect this balanced activity at rest. Previous studies on chronic pain have demonstrated disruption in the temporal and spatial properties of the functional connectivity at rest.[2,6,7,25,28,38]

The goal of the present study was to investigate whether CRPS patients also demonstrate spatial alterations in functional connectivity of the DMN. Furthermore, because of the clinical presentation of CRPS patients, we also investigated the functional connectivity of the S1/M1 and IPS/MIP. We hypothesized that alterations in the functional connectivity of the DMN, S1/M1, and IPS may be related to the clinical parameters of CRPS, that is, the sensory, motor, and autonomic symptoms.

Methods

Participants and Psychophysical Examination

Twelve CRPS patients (5 male, 7 female, mean age 61.08 years ± 11.12 standard deviation [SD]) participated in the study. They met the Budapest criteria for CRPS.[16] In order to minimize any bias, we intentionally performed a consecutive sampling of the patients in our specialized CRPS outpatient clinic. Twelve healthy age- and sex-matched subjects served as a control group (5 male, 7 female, mean age 60.92 years ± 10.96 SD). Patients with affected upper (9 patients) and lower (3 patients) limbs and different duration of CRPS symptoms were examined. The median of duration of CRPS symptoms was 15.5 weeks with a range of 4 to 406 weeks. Ten of the patients had been diagnosed with CRPS I, and 2 with CRPS II by an experienced neurologist (C.M.) in the University Hospital Erlangen. A recent study by Gierthmühlen and colleagues[14] forms the rationale for including CRPS I and CRPS II patients. They investigated sensory signs of CRPS and found that CRPS I and II had almost identical somatosensory profiles, suggesting that the pathophysiology of pain and hyperalgesia is similar.[14] Clinical symptoms were assessed in a standardized neurologic examination before functional magnetic resonance imaging (fMRI) measurement. Sensory symptoms were examined by stroking with a cotton wisp and by gently brushing the skin with a SENSELab TM brush 05 (Somedic, Hörby, Sweden). The examination was performed on both the affected and unaffected limbs, and patients were instructed to report side differences, indicative of hyper- or hypoesthesia. Furthermore, the magnitude of CRPS pain was quantified using the German version of the McGill Pain Questionnaire (MPQ),[37] which was analyzed using the pain rating index (PRI). Motor function was assessed according to the presence of paresis, tremor, and dystonia as observed in a neurologic examination. For the evaluation of autonomic disturbances, the following symptoms were assessed: 1) difference between skin temperature on the affected and unaffected sides. After acclimatization for at least 30 minutes, skin temperature was recorded on the volar aspect of the unaffected and affected limbs with an infrared thermometer Thermo Hunter HR 1 (ASM, Unterhaching, Germany); 2) difference in skin color (red, livid, or white); 3) presence of sweating abnormalities (hypo- or hyperhidrosis); 4) presence of distal edema; and 5) trophic changes in skin, nails, or hair. Spontaneous pain was quantified after the fMRI scan using a numeric rating scale (NRS) ranging from 0 (no pain) to 10 (worst imaginable pain). Table 1 gives a detailed summary of the epidemiologic data of the patients. All subjects were informed about the procedures of the study and gave their informed written consent in line with the Declaration of Helsinki. The study was approved by the local ethics committees of the University of Erlangen.

fMRI Acquisition

Echoplanar images were collected on a 1.5-T MRI scanner (Magnetom Sonata; Siemens, Erlangen, Germany) using the standard head coil and the Siemens Magnetom gradient overdrive. For each subject, the time-series of 90 whole-brain images were obtained using a gradient-echo, echo-planar scanning sequence (repetition time 3 seconds, time to echo 40 ms, flip angle 90°, field of view 220 mm^2, acquisition matrix 64 × 64, 16 axial slices, slice thickness 4 mm, gap 1 mm). A T1-weighted 3-dimensional magnetization-prepared rapid acquisition gradient echo sequence scan (voxel size = 1.0 × 1.0 × 1.0 mm^3) lasting 8 minutes, 21 seconds was recorded for the later overlay between each subject's individual brain anatomy and fMRI data. The fMRI data scan (voxel size = 3.0 × 3.0 × 3.0 mm^3) lasted 4 minutes, 30 seconds and resulted in 90 functional volumes. All subjects were instructed to keep their eyes closed but to remain awake during the fMRI measurement.

FMRI Data Analysis

Data analysis, registration, and visualization were performed with the fMRI software package BrainVoyager