BIOMARKERS OF COMPLEX REGIONAL PAIN SYNDROME REVISITED: A BICENTRIC STUDY

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ABSTRACT

Complex regional pain syndrome (CRPS) is accompanied by brain-wide functional abnormalities, including aberrations in the sensorimotor cortex and thalamus with focal increases in subcortical infra-slow oscillations (ISO), bidirectional changes within the default mode network (DMN) and decrease in global degree rank order disruption index (kD). Here, we aimed to determine the reproducibility of previous results by evaluating the largest cohort so far from two different centers: Greifswald, Germany (N_P/N_{HC} = 38/33) and Sydney, Australia (N_P/N_{HC} = 21/21). Participants underwent a comprehensive clinical examination and brain imaging using a 3T MRI scanner with standard resting-state BOLD fMRI acquisition. After preprocessing and quality assessment, functional connectivity (FC) was evaluated in 51 patients (41/10 women/men [w/m], age 50.3 ±13.7) and 50 HCs (35/15 w/m, age 50.3 ±13.8) using CONN toolbox v. 21a. First, 13 chronic pain-related regions of interest (ROI) were determined. We calculated FC of 9 predefined ROI pairs and explored FC among all ROIs, as well as global changes in DMN and kD. Besides group comparisons, imaging parameters were correlated with pain levels and tactile spatial resolution. Hypotheses and analyses were published prior to data evaluation (https://osf.io/e37td/). Among predefined ROI pairs, we found only weak-to-moderate decrease in FC between the right nucleus accumbens (rNAc) and bilateral ventromedial prefrontal cortex. The unconstrained ROI-to-ROI analysis revealed decreased FC between the periaqueductal gray matter (PAG) and left anterior insula, and increased FC between the right sensorimotor thalamus and rNAc. In the correlation analysis, pain was positively associated with insulo-prefrontal FC, whereas sensorimotor thalamo-cortical FC was positively associated with tactile spatial resolution of the affected side. We found no group differences for kD or FC in the DMN. The kD was, however, positively correlated with the disease duration. In summary, while the previous results were largely not replicated despite the larger sample size, novel findings from two independent cohorts point to potential down-regulated antinociceptive modulation by the PAG and increased connectivity within the reward system as pathophysiological mechanisms in CRPS. The lack of global connectivity changes (kD, DMN) and group-wise alterations in thalamo-cortical FC calls into question their generalizability and potential utility as disease biomarkers.

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KEYWORDS:
neuropathic pain, biomarker, complex regional pain syndrome (CRPS), functional MRI, functional connectivity

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.