Hub maps reveal reduced resting-state connectivity of insular cortex in patients with chronic pain

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Introduction:
A fifth of the western population suffers from chronic pain, the brain pathophysiology of which is still poorly understood. We recently found that patients suffering from chronic pain displayed both temporally and spatially aberrant activity evident in resting-state functional magnetic resonance imaging (fMRI). Seed-based connectivity analysis revealed altered functional connectivity between the patients’ insulae and anterior cingulate cortex (Malinen et al., under revision).

To obtain further measures of brain connectivity in chronic pain, we estimated from the same fMRI data, hub maps that give an intuitive measure of information flow in complex networks (Bassett & Bullmore, 2006). Similar analysis on healthy subjects has identified consistent hubs in brain regions that have high metabolism and are susceptible to amyloid deposition in Alzheimer’s disease (Buckner et al., 2009).

Methods:
We analyzed 10-min runs of 3-T fMRI data from 8 patients (38¬–63 yrs; mean 49; 6 m, 2 f) suffering from chronic pain of different etiologies and from 8 healthy age- and gender-matched control subjects. Subjects were asked to rest quietly in the scanner with their eyes open. We measured 284 functional images (3 x 3 x 4 mm³ voxels, time to repeat 2 s) and a high-resolution anatomical image (1-mm slices, 256 x 256 matrix, field of view 26 cm). Data were realigned, normalized to the Montreal Neurological Institute (MNI) standard space, and smoothed with a 6-mm full-width half-maximum (FWHM) Gaussian filter (SPM2).

We followed the approach of Buckner et al. (2009) by assuming that each voxel in the brain constitutes a vertex in an undirected graph. Edges were drawn between voxels whose de-trended time series were sufficiently strongly correlated (Pearson’s R > 0.25). For each 10-min dataset, we computed a cortical hub map by assigning to each voxel its degree-centrality defined as the number of edges to/from it, normalized by the total number of vertices. We then compared the hub maps between the control and patient groups with a two-sample two-tailed Student’s t-test. Clusters with p < 0.05 (false discovery rate corrected) and an extent of 100 or more voxels were considered statistically significant between groups.

Results:
We found statistically significant differences between the two subject groups in the degree-centrality measure of several brain regions. The most striking differences were seen in the bilateral posterior insulae, and the left anterior insula where the patient group had fewer hubs; Fig. 1 shows the corresponding t-map. The bilateral superior temporal regions and precuneus also differed between the groups.

Our observations agree with the seed-based correlation analysis performed on the same dataset (Malinen et al. under revision). However, unlike in that analysis, we did not observe any connectivity difference in the anterior cingulate cortex (ACC).

Conclusions:
Unlike seed-based analysis, mapping hubs of functional connectivity does not require one to specify regions of interest. However, the robustness of the obtained result with respect to the arbitrary threshold for Pearson’s R, which was used to draw edges between vertices in the graph, remains to be studied.

Our findings show that some, but not all, regions of the affective pain matrix of chronic pain patients may have a decreased role as functional hubs. Whereas similar decrease of connectivity was evident in the posterior insula of both hemispheres, the connectivity of the anterior insula was statistically significantly disrupted only in the left hemisphere. Perhaps the role of the insula in affective processing of pain is reflected in our observation of its decreased global connectivity.
References:
Malinen, S., et al. (under revision), 'Aberrant temporal and spatial brain activation during rest in patients with chronic pain'.
Categories
- Pain and Autonomic Function   (Sensory Systems)