Neural network changes in Fibromyalgia: insula investigated
Increased coupling of executive control network with insula is related to anxiety and pain intensity

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Introduction

Fibromyalgia (FM) is a disabling chronic widespread pain disorder with an unclear underlying mechanism[1]. Neuroimaging studies show evidence of altered functional connectivity in the central nervous system of FM patients, but the precise relationship is also still unclear.

FM patients often experience depressive or anxiety symptoms. These, as well as pain intensity and sensitivity, have been linked to altered functional connectivity in FM[2]. We focused our investigation on functional connectivity between the Default Mode Network (DMN), the Executive Control Network (ECN) and the bilateral anterior insula.[3]

In healthy participants, the DMN is expected to be anti-correlated to the ECN and anterior insula. In FM, some evidence[4] exist for altered connectivity of DMN, ECN and insula, most notably as an increase between DMN and insula. However these results are inconclusive and not clearly replicated. Thus, there is a need to validate findings from previous studies and to clarify which psychological and pain-related factors contribute to changes in FM functional connectivity

Aims
The current study aimed to investigate the connectivity between the bilateral anterior insula, the ventromedial prefrontal cortex and posterior cortex nodes of the DMN, and the bilateral intraparietal sulcus nodes of the ECN.

Research Questions
1) Test the validity of previous findings of altered connectivity between insula and DMN or ECN nodes in a larger sample size; is an altered connectivity modulated by levels of depression, anxiety, pain sensitivity or pain intensity?
2) Explore whether insula, DMN or ECN nodes have altered connectivity with the rest of the brain.
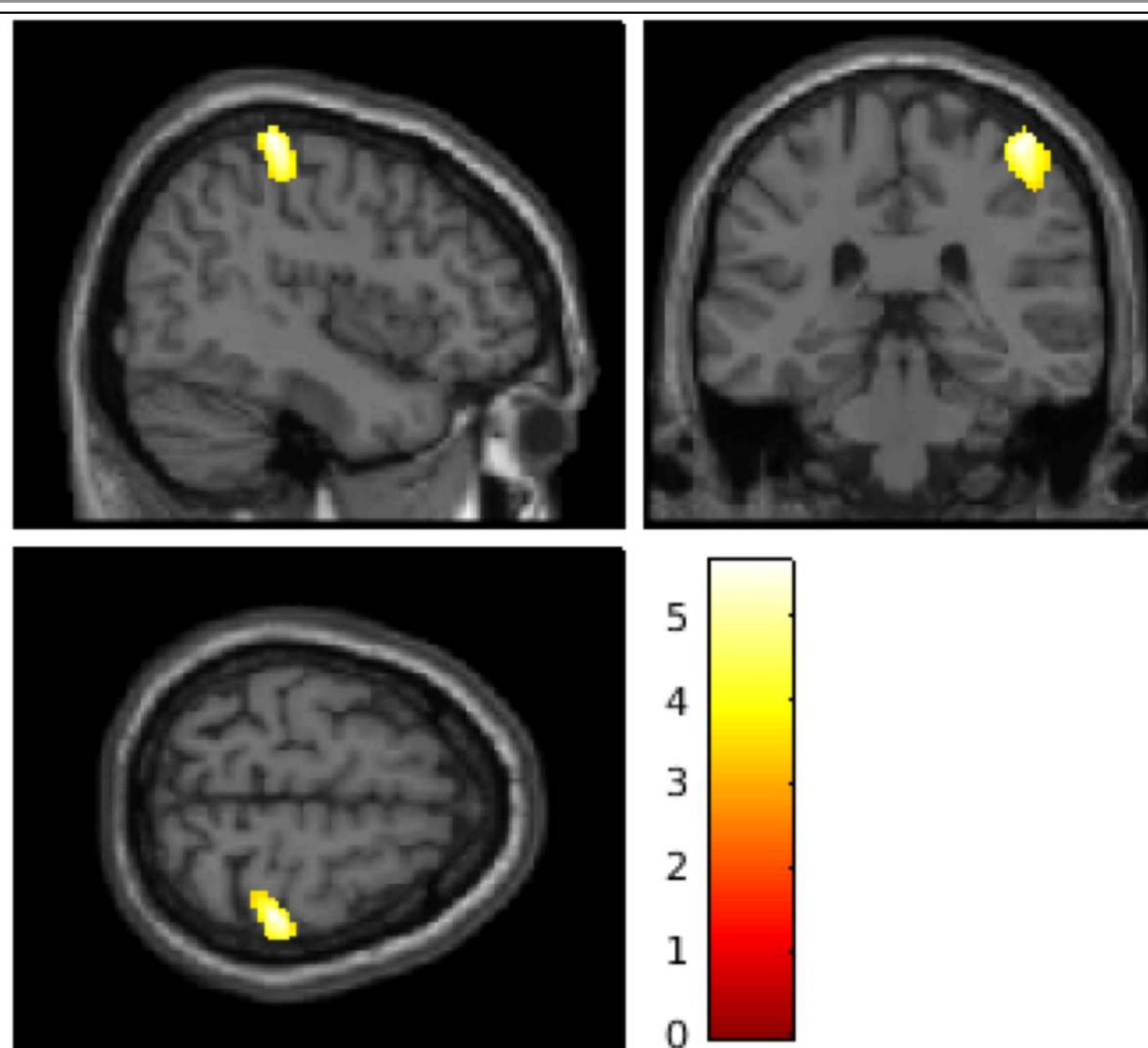
Within FM-group Results

Default mode network was more strongly connected to right sensorimotor cortex in FM with higher depression.
The figure depicts a seed-voxel analysis (seed is ventromedial prefrontal cortex in DMN) and results are significant at p<0.01 FWE-corrected.

Depression scores correlated with PCS rumination for FM (p=0.001).

Methods

Participants: 31 FM patients (1990 ACR criteria) and 29 healthy controls, all female, age-matched (mean 41, range 22-56 years) tested at the Pain and Rehabilitation Centre at the University Hospital in Linköping, Sweden.
The study is part of a large-scale investigation on FM, this study includes clinical examination and pain sensitivity testing from a first visit, and fMRI data collection from a third visit (on average 3.8 months apart)
Exclusion criteria: inability to refrain from NSAID, pain and sleep medication for 48 hrs prior to visit, MR incompatibility, rheumatoid arthritis, metabolic disease, neurologic disease or severe psychiatric condition, malignancy, cardiovascular disease, unregulated thyroid disease, lung disease. For healthy controls: no current pain was reported.
Psychological assessment: Hospital Anxiety and Depression scale (HADS-A and HADS-D), Pain Catastrophizing Scale (PCS) consisting of the subscales rumination, magnification and helplessness
Pain assessment: pain intensity (numeric rating scale 0-10), pressure pain threshold (manual pressure algometer measured average of pressure pain bilaterally in trapezius muscles, erector spine, and tibialis anterior. Pressure increase of 30 kPa/s until perceived pain).
fMRI: 10 min resting state fMRI, Siemens Prisma 3T with 64 channel SENSE headcoil, single shot EPI gradient echo. TR 1.03s
Data preprocessing: Preprocessing with SPM12, normalizing to MNI space, smoothing with 8mm FWHM Gaussian kernel. Motion regressors and scrubbing motion spike parameters (conservative 5% removal with ART toolbox in CONN) were filtered out. Likewise was white matter, CSF and a term for linear detrending filtered out. A band-pass filter (0.008-0.09 Hz) was applied to the data and a component-based noise correction method (aCompCor in CONN) to improve sensitivity and selectivity. Age was modeled as nuisance factor.
Data analysis. Our 6 regions of interest were: posterior cingulate cortex and ventromedial prefrontal cortex from the DMN, left and right intraparietal sulcus from the left and right ECN, left and right anterior insula from the salience network. These were functionally defined ROIs based on neural network template maps from Shirer ea (2012)[6.]. The average time-series within each network was calculated, and correlations of each ROI and the other ROIs (for seed-target analysis) or of each ROI with each voxel in the brain (for seed-voxel analysis) was calculated. ICA analysis in GIFT-toolbox, 20 components, default settings, 100 stability-ensuring reruns of model with ICASSO.

Background

Fibromyalgia (FM) can be defined as chronic (> 3 months) pain widespread over the body with generalized hyperalgesia for mechanical pressure (assessed using tender point examination for at least 11 out of 18 tender points).

The **Default Mode Network (DMN)** is associated with self-referential processing and theory of mind.
The **ECN** is a fronto-parietal **Executive Control Network**, which moderates responses and directs attention.
Anterior insula is part of the salience network and implicated in pain processing.

Functional connectivity changes can be investigated during resting state fMRI in and between intrinsically active neural networks (interconnected regions that contribute to neural functioning). Model-free analysis can be done with independent component analysis (ICA). A-priori defined models can be done with seed-target (region-region) or seed-voxel (region-brain) connectivity analysis.

Between-group Results

FM show higher levels of connectivity of Executive control network with insula
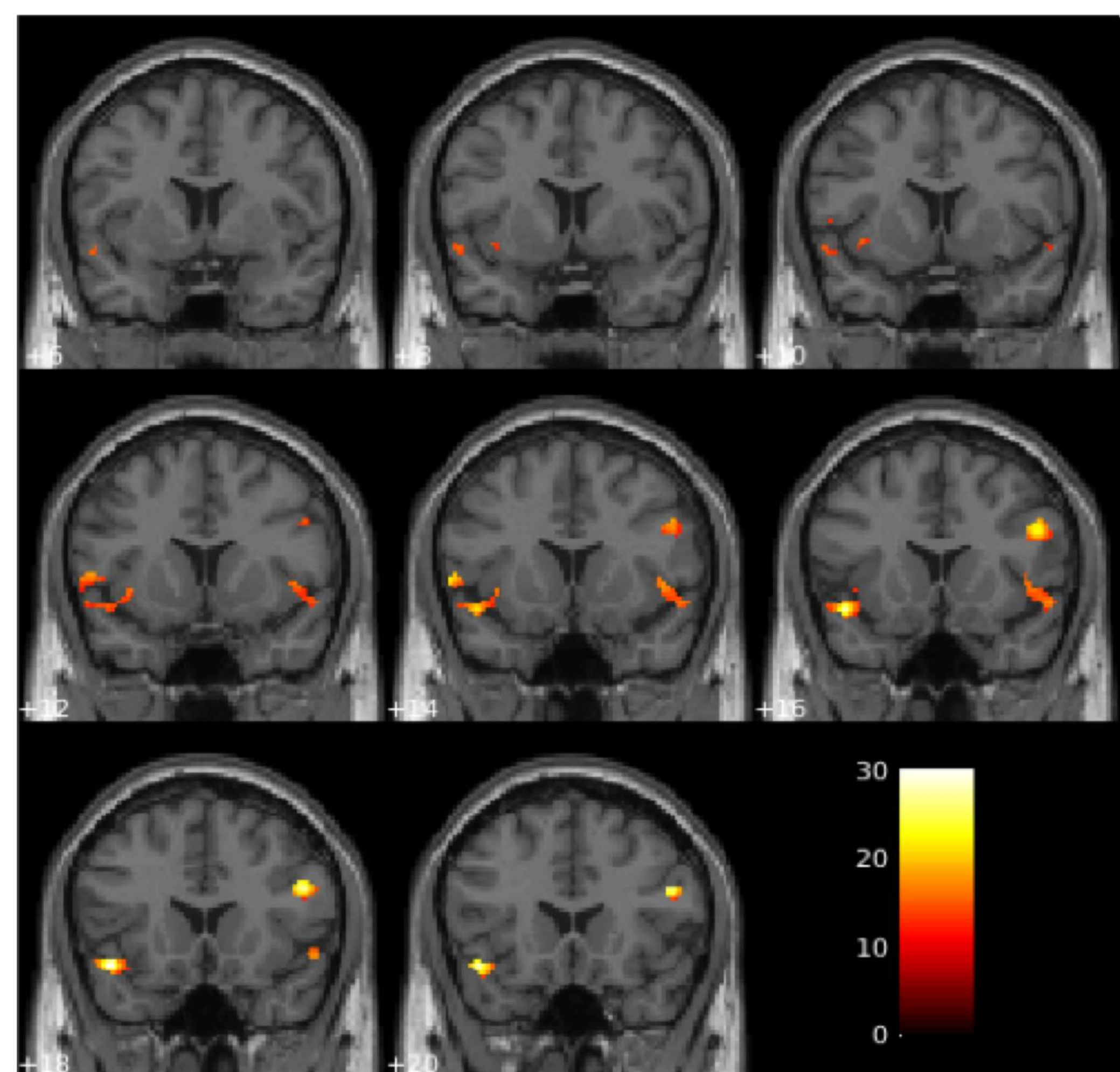
Functional connectivity of the ECN with bilateral insula was higher for patients with FM. This was associated with higher anxiety scores for both FM and healthy controls, and with higher pain intensity within the FM group. The figure depicts a between-group (FM versus controls) independent component analys, of the right ECN component with our regions of interest, significant at p<0.05 FWE-corrected within the regions of interest.
FM patients scored higher than healthy controls on all psychological and pain measurements.

Conclusions

• Our results show that FM have a higher level of connectivity between ECN and insula, but no changes between DMN and insula unlike previous studies.

• Napadow *ea* (2010) found that more connectivity between ECN and insula correlated to stronger intrinsic pain during scanning[5]. Our findings show that stronger pain intensity measured *not at the same day* also can be linked to higher level of ECN-insular connectivity.

• Higher DMN-sensorimotor cortex connectivity has previously also been linked to chronic pain, and may reflect an aspect of pain sensitization.

• Connectivity changes showed to be influenced by anxiety and depression scores, this was in concordance with our hypothesis.

References
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