Functional Connectivity Modulations in Resting State and Offset Analgesia in Chronic Pain Patients: an fMRI Study

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Background & Aims

Chronic pain, often lacking diagnostic peripheral pathology, has been attributed to cerebral dysfunction from recent neuroimaging findings. Here we used functional magnetic resonance imaging (fMRI) to seek for dynamic alterations in cerebral networks between no-pain and phasic-pain conditions in chronic pain patients with various etiologies. Specifically, we made a comparison between chronic pain patients (CP) and healthy controls (HC) in 1) whole-brain functional connectivity (FC) during resting-state, and 2) dynamic FC changes during offset analgesia (OA)/sham paradigms by thermal pain stimulus known to trigger endogenous pain modulation.

Methods

Subjects: 16 CP and age-, gender-matched 16 HC subjects; all were right-handed, free from caffeine or alcohol 24h before the experiment.

Disease	No. of CP	Medication Treatments	No. of CP
Fibromyalgia	7	Tricyclic Antidepressant Drugs	13
Chronic low back pain	2	Anticonvulsant and Antiepileptic Drugs	11
Complex regional pain syndrome	2	Non-Steroidal Anti-Inflammatory Drugs	6
Limb pain	1	Anti-Anxiety Drugs	5
Phantom limb pain	1	Tramadol	3
Cervical syndrome	1	Serotonin-Noradrenalin Reuptake Inhibitors	2
Sciatica	1		
Migraine	1		

Behavioral Measurements: Current pain intensity by visual analog scale (VAS), short-form McGill pain questionnaire (SF-MPQ), PainDETECT, Pain Catastrophizing Scale (PCS), and Beck Depression Inventory (BDI).

Measurements	HC (Mean±SD)	CP (Mean±SD)	P-value
Sex (F/M)	8F/8M	7F/9M	0.733
Age (yr)	42.13±12.54	42.06±10.96	0.988
VAS	0.06±0.25	51.50±27.13	<0.001*
painDETECT	2.13±3.96	17.31±8.26	<0.001*
SF-MPQ	0.19±0.54	15.13±9.38	<0.001*
PCS	4.81±7.37	32.00±12.05	<0.001*
BDI	3.38±4.86	18.5±12.90	<0.001*

Noxious Thermal Stimulus

- 1) Thermal stimulus given on the left volar forearm by a Peltier-type thermal stimulator (PATHWAY, Medoc, Israel) at ramp rates of 56°C/s (up) and 6°C/s (down).
- 2) Baseline temperature: 32°C. T1, 46°C-stimulus (5 s); T2, 47°C-stimulus (5 s); T3, 46°C-stimulus (20 s). Offset, Constant and Short conditions were pseudo-randomly applied 3 times for each.

Resting-state: Subjects were required to keep eyes open for 5 min.

MRI scanner: 3T MRI scanner (GE Healthcare, UK); we got gradient-echo echo-planar MRI images during thermal stimuli and resting-state, and a high-resolution anatomical image.

Data Analysis:

- 1) SPM12 (Wellcome Trust Centre for Neuroimaging, UK) and CONN Toolbox were used for analysis of images.
- 2) OA effects was examined by FC contrasts during T3 at Offset-Constant and Offset-Short.
- 3) **ROI-ROI analysis** and **gPPI analysis** were used to investigate FC modulations across different states and conditions with age and gender as covariates.
- 4) SPSS 23.0 (IBM, USA) was used to examine correlations between FC alterations and behavioral measurements in both CP and HC groups.

References

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Results

A. Connectivity within the default mode network was decreased in CP compared with HC.

MPFC: middle prefrontal cortex

B. Offset vs. no offset. CP showed enhanced emotional but decreased descending modulatory and reward networks. (P<0.01)

C. Pain vs. no pain. CP showed more intense network activities across emotion, descending modulatory, and reward networks. (P<0.01)

D. NAc-IC (=reward system) FC showed negative correlations with multiple scores of pain intensity, emotion, and cognition. (P<0.05)

Conclusions

The present findings imply that chronic pain involves:

- 1) Default mode network weakness;
- 2) Emotional network hyperactivity;
- 3) "Pain matrix" exaggeration;
- 4) Descending pain modulatory and reward system dysfunction