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Do patients with functional chest pain have neuroplastic reorganization of the pain matrix? A diffusion tensor imaging study

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HIGHLIGHTS

- Central hyperexcitability is believed to play a role in functional chest pain.
- Microstructural reorganization of the pain neuromatrix was assessed.
- Microstructural changes were not present in functional chest pain patients.
- This challenges the hypothesis that visceral hypersensitivity is due to central changes.

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ABSTRACT

Background and aims: In functional chest pain (FCP) of presumed esophageal origin central nervous system hyperexcitability is generally believed to play an important role in pain pathogenesis. However, this theory has recently been challenged. Using magnetic resonance diffusion tensor imaging, the aim was to characterize any microstructural reorganization of the pain neuromatrix in FCP patients.
Methods: 13 FCP patients and 20 matched healthy controls were studied in a 3T MR scanner. Inclusion criteria were relevant chest pain, normal coronary angiogram and normal upper gastrointestinal evaluation. Apparent diffusion coefficient (ADC) (i.e. mean diffusivity of water) and fractional anisotropy (FA) (i.e. directionality of water diffusion as a measure of fiber organization) values were assessed in the secondary sensory cortex, cingulate cortex, insula, prefrontal cortex, and amygdala.
Results: Overall, including all regions, no difference in ADC and FA values was found between the patients and controls ($P = 0.79$ and $P = 0.23$, respectively). Post-hoc tests revealed no difference in ADC and FA values of the individual regions. However, a trend of patients having increased ADC in the mid insula grey matter and increased FA in the mid insula white matter was observed (both $P = 0.065$).
Conclusions: This explorative study suggests that microstructural reorganization of the central pain neuromatrix may not be present in well-characterized FCP patients.
Implications: This finding, together with recent neurophysiologal evidence, challenges the theory of visceral hypersensitivity due to changes in the central nervous system in FCP patients.

1. Introduction

Functional chest pain (FCP) of presumed esophageal origin is considered to be the second most common esophageal cause of chest pain, only exceeded by gastro-esophageal reflux disease (GERD) [1,2]. The pain is typically recurrent, leading to numerous hospital admissions, which are mostly without finding of any specific treatable cause of the pain. FCP is associated with reduced quality of life and major socioeconomic costs [3,4]. The Rome III diagnostic criteria described FCP as "episodes of unexplained chest pain that usually are midline in location and of visceral quality, and therefore potentially of esophageal origin" [2]. Exclusion of GERD and dysmotility based appropriate tests is mandatory together with a negative cardiological examination. Furthermore, the criteria have to be fulfilled for 3 consecutive months with symptom onset at least 6 months before diagnosis.

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The pathogenesis of pain in FCP is not clear, but visceral hypersensitivity is proposed to be essential [5,6]. It is evident that more insight into the pain pathogenesis is needed, including distinction between central and peripheral mechanisms, to improve management and develop new treatment options. Several studies of unexplained chest pain have been conducted, but the results are not consistent [5,7–12]. Recently, the electrophysiological evoked brain response to painful esophageal stimuli was evaluated using advanced methods including inverse source modeling, and no evidence of altered central pain processed was observed [13]. However, few studies have explored whether structural changes in the brain are present in FCP.

Magnetic resonance imaging (MRI) with diffusion tensor imaging (DTI) has the ability to assess changes in white and grey matter microstructure not seen by more conventional imaging techniques [14]. Previously we studied the microstructural brain changes in painful chronic pancreatitis patients and found abnormal microstructure in areas involved in visceral sensory processing indicating structural reorganization of the sensory neuromatrix [15]. DTI based measurements of areas involved in visceral sensory processing have, to the best of our knowledge, never been conducted in FCP patients.

We hypothesized that patients with FCP have changes in brain microstructure in areas involved in the processing of visceral pain. The aim of the study was to assess the brain microstructure described by DTI in white and grey matter areas important for pain processing in healthy controls and patients with FCP.

2. Materials and methods

2.1. Subjects

Thirteen patients with a diagnosis of FCP were included from the Department of Cardiology at Haukeland University Hospital. The demographic and clinical characteristics are given in Table 1 and electrophysiological data from these patients were previously reported [13]. The patients fulfilled the Rome III criteria. Inclusion criteria were: (1) normal cardiac evaluation including coronary angiograms, (2) normal upper gastrointestinal evaluation including conventional manometry using a solid-state catheter, 24-hours impedance/pH-metry recording and gastro-esophageal endoscopy. Exclusion criteria were: (1) concomitant medication interfering with sensation (including antidepressants), (2) history or clinical signs of any pulmonary, musculoskeletal or psychiatric disorders, (3) concomitant disease affecting sensation or compromising the patient's safety during participation in the study, and (4) prior surgery to the gastrointestinal tract.

Table 1
Demographic and clinical characteristics of patients and healthy controls.

	Patients ($N = 13$)	Healthy controls ($N = 20$)
Age (years)	50.4 ± 7.5	46.5 ± 13.8
Age (years) gender specific		
Female	51.6 ± 7.4 ($N = 7$)	45.5 ± 16.4 ($N = 11$)
Male	49.0 ± 8.1 ($N = 6$)	47.7 ± 10.8 ($N = 9$)
Disease duration (years)	5.0 (range 0.8–18.0)	N/A
Chest pain – frequency		
Daily	3	N/A
>3 per week	8	N/A
<3 per week	2	N/A
Mean chest pain intensity VAS score	5.7 ± 1.8	N/A
Body mass index	25.3 ± 2.2 kg/m^2	24.1 ± 3.2 kg/m^2
Blood pressure at rest		
Systolic	136.9 ± 11.5 mm Hg	130.2 ± 9.3 mm Hg
Diastolic	83.8 ± 7.2 mm Hg	81.6 ± 7.4 mm Hg
Heart rate at rest	66 ± 7.9 b/min	68.0 ± 10 b/min
Subjects smoking	3/13	1/15
Subjects on any medication	9/13	3/15
Subjects on drugs affecting neural pathways	0/13	0/20

Data are given as mean ± SD. *N*: number. N/A: not applicable. VAS: visual analogue scale (0–10). b/min: beats/minutes.

Twenty healthy controls were recruited by advertisement among employees at Haukeland University Hospital. Inclusion criteria were: healthy and without any symptoms suggestive of cardiac or gastrointestinal diseases, or pain disorders.

All subjects had no contraindications to performance of MRI. The study was conducted according to the Helsinki II declaration and oral and written informed consents were obtained from all subjects. The protocol was approved by the local Ethics Committee (No: REK vest 2010/2561-2).

2.2. Magnetic resonance imaging

All subjects were examined at Haukeland University Hospital in a 3T MR scanner (Signa HDxt, General Electrics, Milwaukee, WI, USA) equipped with an 8-channel standard head coil. Axial T2-weighted FLAIR-sequence images (FOV 25 × 25 cm, matrix 352 × 224, 5 mm slice thickness, whole brain coverage, repetition time 8802 ms, echo time 127 ms, and inversion time 2200 ms) were evaluated for relevant pathology by an experienced radiologist. Axial T1-weighted 3D BRAVO-sequence images (FOV 25 × 25 cm, 320 × 320 matrix, 1.0 mm slice thickness, whole head coverage, flip angle 14°, repetition time 9.0 ms, and echo time 3.6 ms) were obtained for detailed anatomical information. DTI was performed by covering the entire cerebrum and was acquired axially with a single echo diffusion-weighted sequence with eddy current compensation (repetition time 9000 ms, minimum echo time, matrix 128 × 128, field of view 307 mm, slice thickness 2.4 mm, no slice sparing, 40 contiguous slices, 32 diffusion directions, 4 T2 images, and *b*-value used were 0 and 1300 s/mm^2). Prior to each acquisition, automatic whole-volume first order shimming was performed to minimize field inhomogeneity. The DTI examination time was approximately 5 min.

2.3. Analysis of DTI data

DTI measures the magnitude (described by the apparent diffusion coefficient (ADC)) and directionality (described as fractional anisotropy (FA)) of water diffusion in tissues. ADC represents the mean diffusivity of water in all directions, termed isotropic diffusion. In the presence of barriers, such as cell membranes, fibers, and myelin, the diffusion is greater in one direction (anisotropic diffusion). FA provides a quantitative measure of the degree of anisotropic diffusion (FA values range between 0 (isotropy) and 1 (complete anisotropy)), and is high in regularly organized and structured white matter such as the corpus callosum and lower in less organized tissues such as grey matter. For review see [14].

Analyses of the DTI data were done using NordicICE (Diffusion/DTI Module version 2.3, Nordic Imaging Lab, Bergen, Norway) on a voxel-by-voxel basis. From the diffusion-weighted sequence, ADC and FA values in each voxel were calculated. The ADC and FA values were examined in predefined grey and white matter areas of the brain, and the analyses were performed by the same person (ASB). Files were renamed and personal and clinical data were hidden to make the analysis blind to the investigator. The regions of interest (ROIs) are illustrated in Fig. 1 and were: White matter in relation to (1) anterior, (2) mid and (3) posterior insula, and grey matter of (4) amygdala, (5) anterior, (6) mid and (7) posterior cingulate cortex, (8) anterior, (9) mid and (10) posterior insula,