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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,

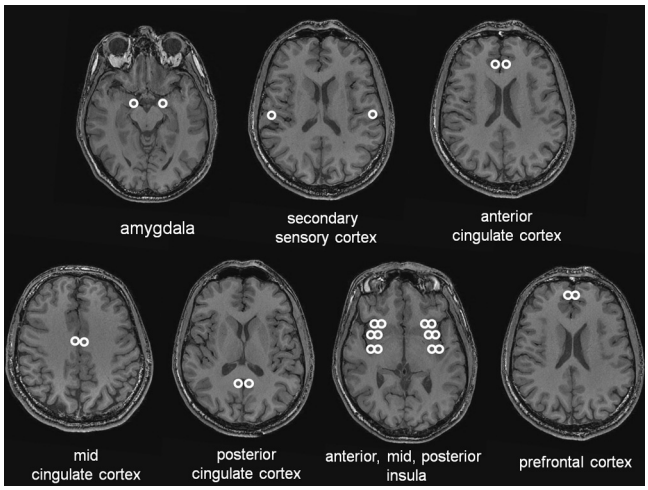

Fig. 1. Illustration of the anatomical positions of the analyzed areas involved in processing of visceral pain. White matter substance was analyzed in the anterior, mid and posterior insula. Grey matter substance was analyzed in amygdala, secondary sensory cortex (SII), cingulate cortex (anterior, mid and posterior), insula (anterior, mid and posterior), and prefrontal cortex.

(11) prefrontal cortex, and (12) secondary sensory cortex (SII). DTI parameters were retrieved from bilateral corresponding (i.e. left and right) brain areas, separately.

The anatomical and DTI data were imported into NordicICE, and the DTI module was utilized for computing the FA and ADC maps. The FA and ADC maps where co-registered yielding a map where anatomical structures could be identified. Each ROI was identified using a standardized procedure: First, the area was found and drawn on the co-registered ADC and FA map. Second, the retrieved location was checked by viewing the anatomical scan, thus securing the highest accuracy in placing the ROI in the correct anatomical area. The ROI position was then saved for later retrieval. This procedure was repeated for all areas, which were then used to extract appropriate mean values of the individual ROIs from the FA and ADC maps.

2.4. Statistics

Results are expressed as mean ±SD. The difference in age and gender distribution between patients and controls was analyzed using *t*-test or Fishers exact test as appropriate. To analyze differences in ADC and FA values, a multivariate analysis of variance (MANOVA) was applied with the subject groups (patient vs. control) as fixed factor, the right vs. left side and gender as co-factors and the ADC/FA values of the ROI locations as dependent variables. The ROI positions were selected a priory and the MANOVA model accounted for multiple tests in the computations. This approach was used to limit the likelihood of type II errors which would result in truly important differences being deemed non-significant [16]. Normality was checked by QQ-plots and the assumption of variance homogeneity by Levene's test. *P*-values less than 0.05 were considered significant. SPSS Statistics 17.0 (SPSS Inc., Chicago, IL, USA) was used for the analysis.

3. Results

Age and gender were comparable between groups (age: $P = 0.18$; gender: $P = 1.0$) (Table 1). Expert evaluation of the MR images concluded that all subjects had normal age-related findings (no excessive atrophy or white matter lesions). No other pathological findings were seen. None of the few white matter lesions were located in or near the ROIs of the FA and ADC measurements.

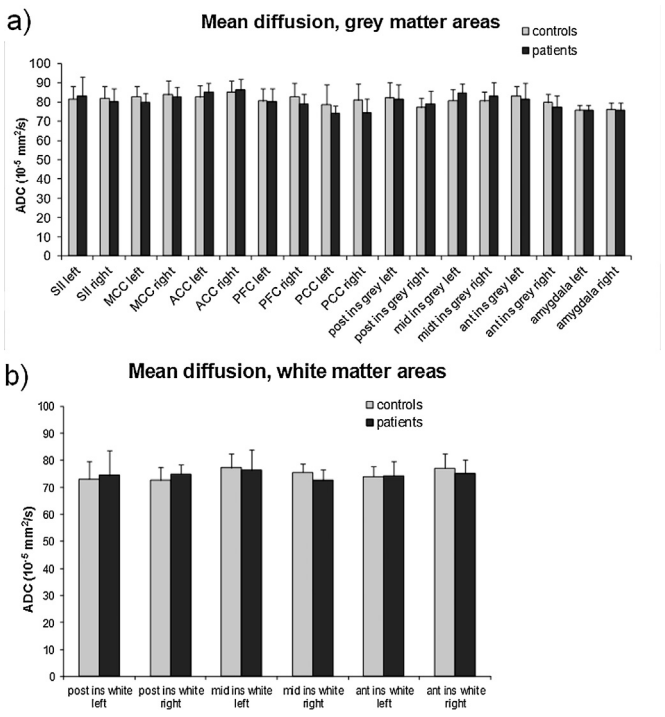

Fig. 2. Mean water diffusivity (expressed as apparent diffusion coefficient (ADC)) of patients with functional chest pain and healthy controls is presented. Grey (a) and white (b) matter regions of interest are known to be involved in the processing of visceral pain. SII: secondary sensory cortex, MCC: mid cingulate cortex, ACC: anterior cingulate cortex, PFC: prefrontal cortex, PCC: posterior cingulate cortex, post: posterior, ant: anterior, ins: insula.

3.1. ADC measurements, mean diffusion

The mean ADC values of all ROIs are shown in Fig. 2. Overall, no difference in ADC values was found between the patients and controls ($F = 0.65$, $P = 0.79$). No side (left vs. right) or gender differences were observed ($P = 0.15$ and $P = 0.82$, respectively). The subsequent univariate tests revealed a trend of patients having increased ADC in the mid insula grey matter ($F = 3.5$, $P = 0.065$), while clearly no differences between the two groups were found in the other regions (all *P*-values > 0.15).

3.2. FA measurements, fiber organization

The mean FA values of all ROIs are given in Fig. 3. No overall differences in FA values were found between the patients and controls ($F = 1.34$, $P = 0.23$). No side (left vs. right) or gender differences were observed ($P = 0.22$ and $P = 0.81$, respectively). The univariate tests showed a trend of patients having increased FA in the mid insula white matter ($F = 3.5$, $P = 0.065$), while no differences between the two groups were found in the other regions (all *P*-values >0.09).

4. Discussion

In well characterized patients with functional chest pain of presumed esophageal origin, we found no significant microstructural changes in grey and white matter areas known to be involved in the processing of visceral pain. The method has proved to be valid by previously identifying microstructural changes of the sensory neuromatrix in both patients with painful chronic pancreatitis and in diabetic neuropathy [15,17]. The results of this explorative study therefore support recent electrophysiological studies where no evidence of altered central pain processing was observed [13]. Hence,

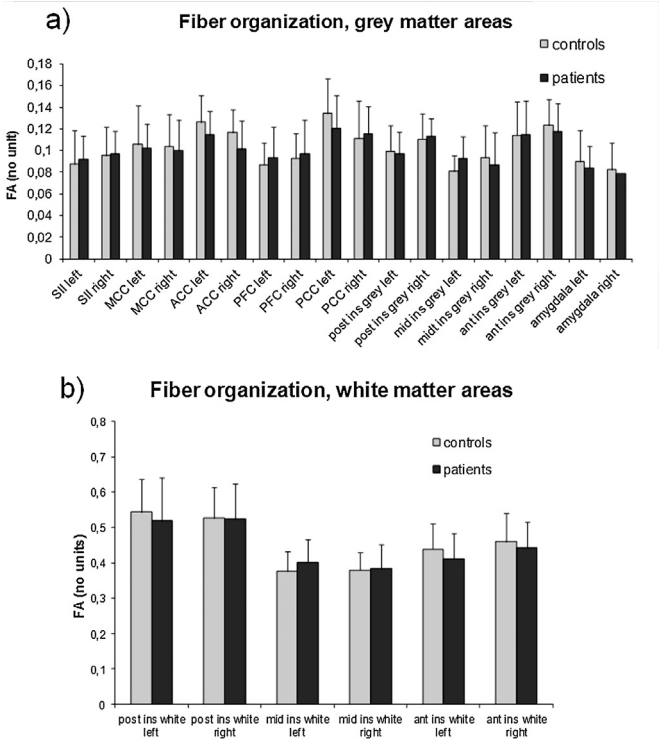

Fig. 3. Degree of fiber organization (expressed as fractional anisotropy (FA)) of patients with functional chest pain and healthy controls is presented. Grey (a) and white (b) matter regions of interest are known to be involved in the processing of visceral pain. SII: secondary sensory cortex, MCC: mid cingulate cortex, ACC: anterior cingulate cortex, PFC: prefrontal cortex, PCC: posterior cingulate cortex, post: posterior, ant: anterior, ins: insula.

the proposed theory of visceral hypersensitivity by central mechanisms in functional chest pain has been further challenged.

4.1. Methodological considerations

DTI measures the magnitude (described as ADC) and directionality (described as FA) of water diffusion in tissues. The exact nature of the neurostructural changes responsible for increased ADC and reduced FA is not clear, but the most accepted hypothesis is that the integrity of the myelin sheath and axonal membrane is reflected by restriction of diffusion perpendicular to the fibers, whereas the integrity of intra-axonal structures (such as microtubules) is reflected by diffusion parallel to the fibers [14]. Decreased FA is a common feature of several diseases associated with neuronal abnormalities, such as schizophrenia, depression, chronic alcohol use, Alzheimer's disease, and diabetes [14,18,19].

The selection of ROIs in this study was hypothesis driven and based on knowledge of visceral sensory processing [20,21]. This design has proven to be valid in our previous study of painful chronic pancreatitis and diabetic neuropathy [15,17]. Hence, the selected brain areas are involved in the so-called "sensory brain matrix". The amygdala receives projections from the spinolimbic tracts and has a role in regulating the affective/motivational component of pain [22–24]. The prefrontal cortex and anterior cingulate cortex (ACC) are strongly connected and receive projections from the thalamus and other limbic and subcortical structures, which are also central in the processing of visceral pain [24,25]. The prefrontal cortex is mainly involved in cognitive operations relating to the pain experience. Generally, SII activation has been suggested to be involved in attention and rating of strength and quality of pain, insula is involved in integration of visceral sensory and motor function, and cingulate gyrus (including ACC) is involved in the emotional, affective/cognitive response to pain [26–32].

Patients with functional chest pain are often poorly defined and likely a very heterogeneous group. The strength of our study is the strict selection of patients according to the current Rome III criteria for FCP [2]. We systematically excluded patients with burning chest pain, patients having symptoms or findings indicative of erosive-/non-erosive gastroesophageal reflux disease, and patients having achalasia or esophageal hypercontractile disorders possibly causing pain. Compared with previous studies we had a very homogenous study population. However, due to these restrictions the numbers of participants with "uncontaminated FCP" were small, which carries a risk for type II errors.

An important thing to consider in a study of brain microstructure is if the disease is of sufficient duration for anatomical changes to develop. In the current study ROME III guidelines have been followed requiring that symptoms have been present at least 6 months. If this is sufficient time for microstructural CNS changes to occur is not presently known.

4.2. Visceral sensory processing in patients with functional chest pain

In previous studies exploring pathophysiology of FCP in details, patients have been proposed to have altered central pain processing [5,7–12]. Results from the studies were mainly based on electrophysiology and are conflicting as both faster and slower conduction of pain signals have been measured (corresponding to either hyper- or hyposensitivity). The reason for these discrepancies could be that the studies are subject to bias since they failed to exclude patients affected by other conditions known to change visceral sensation, e.g. (1) concomitant GERD, (2) significant mental illness, e.g. anxiety or depression, or (3) treatment with antidepressants or analgesics [33–36]. Hobson et al. examined a group of non-cardiac chest pain patients where GERD patients (several with severe pathological DeMeester scores) were included and mental status not assessed [12]. In this study it was proposed that non-cardiac chest pain patients could be divided into groups of phenotypic subclasses: Those with (1) reduced pain thresholds and normal to fast conduction of pain signals, (2) reduced pain thresholds but slow conduction of pain signals, and (3) normal pain thresholds. The results leading to Hobson's groups 1 and 2 could be a bias of the GERD subpopulation or included anxious patients as both conditions can induce central sensitization [12]. None of the patients in the current study had GERD or depression/anxiety, so it was not surprising that all would be classified into Hobson's group 3 [13]. In contrast Hollerbach et al. examined a better characterized population of 8 non-cardiac chest pain patients where GERD was excluded by pH-metry and no drugs interfering with sensation was accepted [5]. In this study patients had lower thresholds for sensation in the esophagus and shorter latencies on cortical evoked pain response, which would be expected if patients were hypersensitive/hypervigilant. However, no upper endoscopy was performed and thus it was not controlled for concomitant esophageal diseases, which could have biased results towards hypersensitivity. In contrast the study by Smout et al. demonstrated longer latencies and lower amplitudes of evoked cortical potentials in 10 patients with non-cardiac chest pain patients using rapid balloon distension [37]. However, again patients were not comparable to the current study population as all had esophageal motor disorders and chest pain, and upper endoscopy/pH monitoring were not done. Frobert et al. examined 10 patients with syndrome X in a patient population similar to functional chest pain, who had normal upper endoscopies and measured normal latencies but reduced amplitudes of evoked brain potentials following esophageal electrical stimuli [38]. However, no exclusions were made of pH-study pathology, depression

and anxiety, or medication potentially interfering with sensation. In line with these conflicting finding we recently conducted an electrophysiological study where we found no differences between patients with well-characterized FCP and controls in resting state electroencephalogram, evoked brain potential characteristics and brain electrical sources [13].

To sum up, several studies have proposed that patients with FCP have altered cerebral processing of esophageal pain. However, the studies are not in agreement of whether the CNS response is increased, decreased, or unchanged. This can largely be explained by the bias of GERD subpopulations, pain modulating medication, anxiety/depression, and small and heterogeneous patient groups. Although our study assessed structural rather than dynamic/functional changes we question central mechanisms (evident as microstructural reorganization) as cause of chest pain, a view supported by the lack of consensus in the previous electrophysiological studies. Alternative possible etiologies of relevance in the induction of pain in these patients could be peripheral changes such as abnormal contractions in the esophageal muscles which as such these may not evoke permanent changes in the CNS [39]. Another possibility is that the functional chest pain patients have changes in the sensitivity only in the time periods of their pain attacks. Such a short lasting pain may not be sufficient in causing long lasting or permanent changes in the CNS. Furthermore, it cannot be excluded that findings from previous electrophysiological studies may be related to other yet unknown pathophysiology in peripheral tissues and nerve afferents, which will invariably affect characteristics of evoked brain potentials.

5. Conclusions

Our findings in this explorative study suggest that microstructural reorganization of the central pain neuromatrix may not be present in well-characterized functional chest pain patients. The mechanism of pain and whether it originates in the esophagus or in the central nervous system is still unknown, and further studies on well-characterized patient groups are highly warranted.

Conflict of interest

All authors declare no conflicts of interest.

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Author contribution: DALH performed the investigation; DALH and JGH recruited the patients; ALK, DALH, GD, AMD, JBF designed the study; ASB, JBF analyzed the data; JBF, ASB, DALH, ALK, AMD wrote the paper.

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