Reduced Cortical Thickness of Brain Areas Involved in Pain Processing in Patients With Chronic Pancreatitis

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BACKGROUND & AIMS: Patients with painful chronic pancreatitis (CP) might have abnormal brain function. We assessed cortical thickness in brain areas involved in visceral pain processing. **METHODS:** We analyzed brain morphologies of 19 patients with painful CP and compared them with 15 healthy individuals (controls) by using a 3T magnetic resonance scanner. By using an automated method with surface-based cortical segmentation, we assessed cortical thickness of the primary (SI) and secondary (SII) somatosensory cortex; prefrontal cortex (PFC); frontal cortex (FC); anterior (ACC), mid (MCC), and posterior (PCC) cingulate cortex; and insula. The occipital middle sulcus was used as a control area. The pain score was determined on the basis of the average daily amount of pain during 1 week. **RESULTS:** Compared with controls, patients with CP had reduced overall cortical thickness ($P = .0012$), without effects of modification for diabetes, alcoholic etiologies, or opioid treatment (all P values $>.05$). In patients with CP, the cortical thickness was decreased in SII ($P = .002$, compared with controls), PFC ($P = .046$), FC ($P = .0003$), MCC ($P = .001$), and insula ($P = .002$). There were no differences in cortical thickness between CP patients and controls in the control area ($P = .20$), SI ($P = .06$), ACC ($P = .95$), or PCC ($P = .42$). Cortical thickness in the affected areas correlated with pain score ($r = 0.47$, $P = .003$). **CONCLUSIONS: In patients with CP, brain areas involved in pain processing have reduced cortical thickness. As a result of long-term, ongoing pain input to the neuromatrix, cortical thickness might serve as a measure for overall pain system dysfunction, as observed in other diseases characterized by chronic pain.**

Keywords: Magnetic Resonance Imaging; Neuroplasticity; Reorganization; Pain Response.

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In a majority of patients with chronic pancreatitis (CP), abdominal pain represents a significant clinical problem and its management a major challenge. The pain is typically ongoing with recurrent pain attacks and is associated with malnutrition, physical and emotional disability, and reduced quality of life.[1] The treatment of CP pain is often ineffective and disappointing, which leads to a search for optimized treatment based on a better understanding of underlying pain mechanisms.

Traditionally, the pain in CP has been ascribed to the diseased pancreas itself, ie, ongoing inflammation, pseudocyst formation, and ductal abnormalities with increased ductal and parenchymal pressure.[2] However, in many of these patients, there is histologic evidence of nerve damage.[3,4] Previous studies have also reported sensitization of the central nervous system and reorganization of brain areas involved in visceral pain processing.[5–11] Furthermore, microstructural changes in pain-related brain areas assessed by magnetic resonance diffusion tensor imaging have been described. These findings support accompanying structural reorganization of the neuromatrix as also seen in other diseases characterized by chronic pain.[11] However, the exact mechanisms behind both of these functional and structural changes are still not completely understood.

Recently, advanced cortical thickness analysis based on magnetic resonance imaging (MRI) of the brain has been applied in the study of pain mechanisms, with demonstration of pain-related cortical changes in diseases such as irritable bowel syndrome and trigeminal neuropathic pain.[12–14] Improved methods for automated extraction of the cortical boundaries allow accurate, robust, and rapid analysis of cortical thickness,[15–17] which positions cortical thickness analysis as an effective and easy applicable tool for assessing changes in the central pain system. To our knowledge, cortical thickness analysis has not been reported in CP patients.

We hypothesized that CP patients with sustained abdominal pain have changes of cortical thickness in areas involved in visceral pain processing. The aims of the study were (1) to compare cortical thickness in areas involved in visceral pain processing in healthy controls and CP patients and (2) to correlate the findings in patients with the clinical pain data.

Methods

Subjects

Nineteen patients with CP from the Department of Gastroenterology and Hepatology, Aalborg Hospital were included. The diagnosis of CP was based on the Mayo Clinic diagnostic criteria.[18] The inclusion criteria were abdominal pain

Abbreviations used in this paper: ACC, anterior cingulate cortex; ANOVA, analysis of variance; CP, chronic pancreatitis; FACE, Fast Accurate Cortical Extraction; FC, frontal cortex; MCC, mid cingulate cortex; MRI, magnetic resonance imaging; PCC, posterior cingulate cortex; PFC, prefrontal cortex; ROI, region of interest; SI, primary somatosensory cortex; SII, secondary somatosensory cortex.

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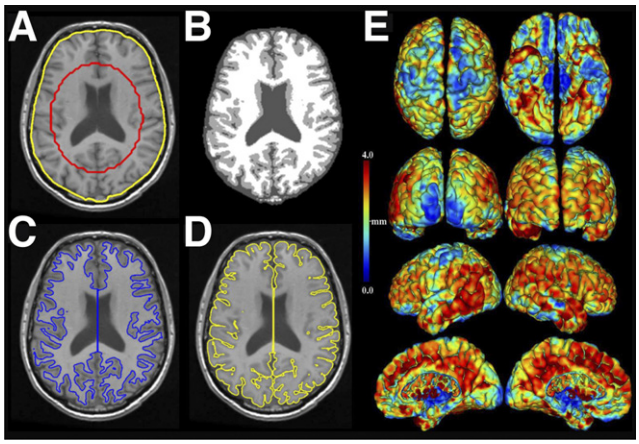

Figure 1. Steps in the cortical thickness analysis with extraction of the cortical boundaries. (*A*) Spatially aligned MRI data with initiating extraction contours superimposed. (*B*) Brain tissue classified as white and gray matter and cerebrospinal fluid. (*C*) White and (*D*) gray matter surfaces superimposed on MRI data. (*E*) The cortical thickness distribution of a healthy subject is shown.

typical for pancreatitis (ie, dull epigastric pain, eventually radiating to the back) and chronic pain (ie, pain ≥3 days per week for at least 3 months). Both patients on stable opioid medication and patients on nonopioid analgesics were included. Patients with other acute or chronic pain syndromes (eg, irritable bowel syndrome and lower back pain) were excluded. The intensity of pain was graded by using the diary pain scores (on the basis of a 0 to 10-cm visual analogue scale), with assessment of daily average pain for 1 week before investigation. The pain was reported without any pause in medication.

Fifteen healthy volunteers were recruited as controls from hospital and university staff. They received no medication and did not have any gastrointestinal symptoms or pain-related diseases. Subjects had no contraindications to MRI. The local Ethical Committee approved the study protocol (N-20080028MCH).

Cortical Thickness Analysis

The method for cortical thickness analysis, Fast Accurate Cortical Extraction (FACE), is described in detail by Eskildsen et al.[16,17] In brief, the analysis allows measurements of the cortical thickness distribution throughout the entire cortical surface on the basis of high-resolution 3D MRI (Figure 1), including average data for the entire hemispheres and individual anatomic regions of interest (ROIs) according to the Montreal Neurological Institute system.[19] The method is described in Supplementary Material.

The ROIs included in the present study were hypothesis-driven on the basis of previous studies and the knowledge of the processing of visceral pain[11–13,20]: (1) primary somatosensory cortex (SI) defined as the postcentral gyrus, (2) secondary somatosensory cortex (SII) defined as the Rolandic operculum, (3) dorsolateral prefrontal cortex (PFC) defined as the middle frontal gyrus, (4) laterofrontal cortex (FC) defined as the orbital parts of the superior and inferior frontal gyrus, (5) cingulate cortex defined as the anterior (ACC), mid (MCC), and posterior (PCC) divisions of the cingulate cortex, (6) insula defined as the entire insula, and as control area, (7) occipital middle sulcus.

Statistics

All results are expressed as mean ± standard deviation. Differences in age, gender distribution, and structural MRI findings were analyzed by using Student *t* test or Fisher exact test as appropriate. The differences in cortical thickness between CP patients and controls were compared by a 3-step procedure. First, the overall differences in cortical thickness were compared by Student *t* tests. The retrieved differences were further adjusted in a subanalysis (two-way analysis of variance [ANOVA]), with stratification for opioid treatment, diabetes mellitus, alcohol etiology, and pain pattern (continuous vs attack-wise) of CP. Third, for each ROI a mixed ANOVA model was used to analyze differences in cortical thickness, with side (right vs left) as a within-subject factor and group (CP vs controls) as a between-subject factor. For each ROI the mixed ANOVA model accounted for multiple significances in the computations. This approach was used because it limits the likelihood of type II errors, which would result in truly important differences being deemed nonsignificant.[21] Normality was checked by QQ-plots and the assumption of variance homogeneity by the Levene test. Correlations between cortical thickness values and clinical parameters (Table 1) and between the dose of analgesics (morphine equivalents) and pain intensity were analyzed by using the Pearson correlation coefficient. *P* values <.05 were considered significant. The software package Stata version 11.2 (StataCorp LP, College Station, TX) was used for the statistical analysis.

Results

The study was completed by all subjects. The demographic and clinical characteristics are given in Table 1. Age and gender were comparable between groups (all *P* values >.05). Two patients had previous surgery with partial pancreatic resections. All

Table 1. Demographic and Clinical Characteristics of Patients and Healthy Volunteers

	Chronic pancreatitis (n = 19)	Healthy volunteers (n = 15)
Age, *y* (range)	52 (25–68)	47 (30–64)
Males, no. (%)	15 (79)	9 (60)
Etiology, no. (%)[a]		
Toxic-metabolic (alcoholic)	11 (58)	
Idiopathic	5 (26)	
Genetic	2 (11)	
Autoimmune	0 (0)	
Recurrent and severe acute pancreatitis	1 (5)	
Obstructive	0 (0)	
Diary pain score (visual analogue scale, 0–10)		
Average pain	3.6 ± 2.0	
Dose of analgesics (morphine equivalents) (*mg*)	52.8 (range, 0–210)	
Duration of chronic pancreatitis (*mo*)	95 ± 45	
Diabetes mellitus, no. (%)	6 (32)	0 (0)

NOTE. Data are mean ± standard deviation.
[a]According to the TIGAR-O classification system.[39]