Systematic mechanism-orientated approach to chronic pancreatitis pain

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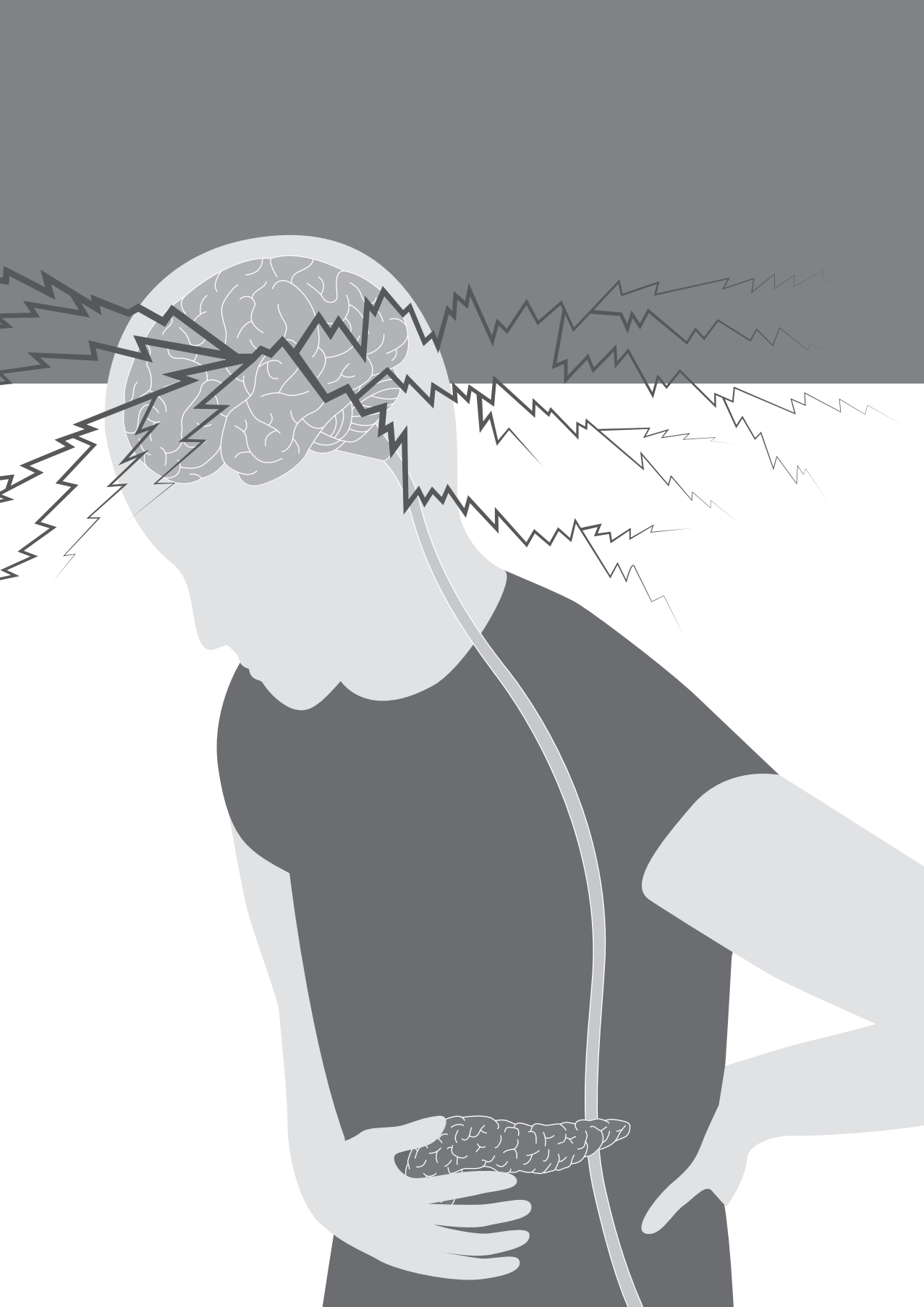

Chapter 1

General introduction

Epidemiology

Chronic pancreatitis is a disease involving progressive inflammatory changes in the pancreas, usually leading to impairment of endocrine and exocrine function.[1] Taking the data for European countries together, the incidence is approximately 6.0 per 100.000 inhabitants.[2] Around 80% of patients with chronic pancreatitis are male and the peak incidence is between 45 to 54 years.[2] Chronic pancreatitis is a poorly understood disease, a major source of morbidity – and costly.[3,4] The most important reason for admission to the hospital is to manage acute flares of inflammation with severe pain, malnutrition and treatment of complications like pancreatic duct strictures and pseudocysts.[5] Admission rate to the hospital has shown a steady increase in the last decade, and has an incidence of 8.5 per 100.000 person-years.[6] The overall 10 and 20-year survival rate is 70% and 45%, respectively, which rates are significantly lower compared to the standard population.[4] Most deaths are not directly related to chronic pancreatitis but to cardiovascular disease and lung cancer, the result of alcohol abuse and smoking.[7] These addictions are frequent in chronic pancreatitis patients.

Etiology

Traditionally the etiology of chronic pancreatitis has been divided into three categories: alcohol, idiopathic and 'other'. In Western countries alcohol abuse is the major cause of chronic pancreatitis accounting for up to 70 - 80% of all cases.[8] Idiopathic pancreatitis accounts for 20% of cases and the remaining 10% is categorized as 'other' i.e. trauma, pancreas divisum, hyperparathyroidism and autoimmune pancreatitis. More recently a more extensive classification system has been described; TIGAR-O, which is an acronym for: toxic-metabolic (T), idiopathic (I), genetic (G), auto-immune (A), recurrent (severe) acute pancreatitis (R) and obstructive mechanisms (O).[9] Other causes are tropical pancreatitis and systemic diseases such as systemic lupus erythematous. Another classification system often used, the M-ANNHEIM classification system, combines etiology, clinical stage and severity of the disease.[10]

Pain

Pain is the leading symptom in chronic pancreatitis. Almost every chronic pancreatitis patient experiences short or long periods of pain during the disease course. The pain is typically located in the epigastrium, radiating to the flanks and back and described as vague to intense and boring. Patients often relate food intake, physical activity and psychological stress to increase of pain. Different pain patterns have been described varying from pain attacks with pain free intervals to continuous severe pain. Exact numbers regarding analgesia use in chronic pancreatitis are lacking, however high dosage opioid use and opioid dependence are not uncommon in typical clinical practice.[11]

Pathophysiological mechanisms

Three groups of pathophysiological mechanisms have been suggested to cause pain in chronic pancreatitis: 1) inflammation of the pancreas (e.g. upregulation of inflammatory mediators, neuropeptides and growth factors); 2) increased intrapancreatic pressure within the parenchyma and/or pancreatic duct, causing tissue ischemia (e.g. pancreatic duct strictures or stones); and 3) (late) pancreatic and extrapancreatic complications (e.g. pseudocysts, portal thrombosis, bile duct/duodenal strictures and peptic ulcers).[12-17]

Pain management

Pain management in chronic pancreatitis is conventionally aimed at dealing with the source of the pain. The initial step includes correction of pancreatic insufficiency and life-style advice. If such measures are not successful, the next step is typically symptomatic treatment with analgesics based on the 'pain relief ladder' provided by the World Health Organization.[1,18] In the absence of satisfactory pain relief, the following step in the treatment strategy involves endoscopic therapies, usually performed for pancreatic duct strictures and pancreatic duct stones. Eventually patients in whom opioid therapy and endoscopic treatment have failed and pain persists are referred for surgery. This usually aims to drain the pancreatic duct with or without resection of an inflamed part of the pancreas. The reported success rate in terms of pain reduction by endoscopy or surgery varies considerably, ranging from good to poor results, and is accompanied by much debate regarding optimal timing of these interventions.[19]

However, even when the reason for pain seems obvious in the sense of a clear source of nociception, and even though this source (e.g. an inflammatory mass, a chronic cyst or a dilated main duct) appears to have been effectively treated, chronic pancreatic pain may persist.[20,21] It thus seems plausible that the pain in chronic pancreatitis is not (only) due to the pancreas as a nociceptive source, but also due to changes in transmission of painful inputs emanating from the pancreas, i.e. damage to nerves innervating the pancreas, and changes in pain processing by the central nervous system, as is also reported for other chronic visceral pain syndromes.[22]

Peripheral sensitization

Alterations indicative of nerve damage, e.g. increased number and diameter of pancreatic nerves, and inflammation of perineural sheathes have been described in chronic pancreatitis.[17,23-25] Tissue damage accompanying chronic pancreatitis leads to an increase of inflammatory mediators (e.g. nerve growth factors, brain-derived neurotrophic factors and proinflammatory cytokines). These mediators together with neural alterations will lead to an increase of excitability of nerves innervating the pancreas.[26,27] Ongoing inflammation of the pancreas with local complications will lead to an aggressive barrage

of nociceptive input to nociceptors which subsequently become more sensitive to further stimulation.[28,29] This sensitization of nociceptors and nerve transmission (peripheral sensitization) has been shown to correlate with clinical pain scores and thus seems to play an important role in maintaining pain in chronic pancreatitis.[30]

Central sensitization

Further sensitization, now of central pain processing, starts in the spinal cord where increased synaptic efficiency in neurons of the dorsal horn of the spinal cord and later of supraspinal sites develops following ongoing noxious stimulation. Such central sensitization due to ongoing painful input manifests itself as an increase in pain experience (hyperalgesia). Ultimately even non-painful inputs may become painful (allodynia). Convergence between visceral and somatic afferents in the spinal cord may lead to segmental or spreading hyperalgesia outside the area of injury.[31-35] From the spinal cord visceral pain transmits to the brain through the spinothalamic tract to the thalamus. From the thalamus projections to the insula, amygdala, hypothalamus as well to the secondary somatosensory cortex, prefrontal cortices and cingulate have been observed. Cortical reorganization and functional changes in these areas and the brainstem are observed in the presence of chronic pancreatitis pain, suggesting a central neurodegenerative response to pain.[36] Such pain is particularly aggressive regarding induction of central sensitization and somatotopic alterations due to the interaction of ongoing nociceptive input with increased excitability of neurons and decreased efficacy of inhibitory mechanisms. Alternative routes to central sensitization are high humeral concentrations of inflammatory mediators sensitizing peripheral nerves and the central nervous system.[37] Finally, an autonomous state can be induced where pain is no longer dependent on (or driven by) the presence or intensity of a noxious peripheral stimulus.

Descending pain modulation

Descending pain modulation can lead to either an increase in the spinal transmission of pain (facilitation) or a decrease in its transmission (inhibition). The balance between the two states determines the perception of pain and central sensitivity to pain. Multiple regions of the central nervous system are involved in this process such as the periaquaductal grey, the rostroventromedial medulla and the limbic system. An example of descending pain modulation ('pain inhibits pain', a response to a noxious stimulus is inhibited by another noxious stimulus) is conditioned pain modulation - CPM (formerly known as diffuse noxious inhibitory controls (DNIC)). When central sensitization is present descending mechanisms often fail, due to a decreased activity in the inhibitory pathway of the spinal cord and an increase in facilitatory pathways, resulting in a further increase in pain.[31-33,38,39]

Implications

It is clear from the above that the problem of pain in chronic pancreatitis is often not restricted to consideration of local, peripheral pancreatic pathology. In the pain of chronic pancreatitis, downstream extrapancreatic alterations in peripheral – and most importantly – central pain processing play a key role. This role must not be neglected if we are to achieve adequate understanding of the phenomenon of chronic pancreatitis pain resistant to adequate therapeutic measures targeting or deafferenting only the nociceptive source – i.e. the pancreas. Hence, a fourth point should be added to the earlier mentioned three mechanisms underlying the pathophysiology of pain in chronic pancreatitis: 4) alterations in the transmission of pain inputs by pancreatic nerves and the subsequent processing of pain by the central nervous system.

In summary, altered central pain processing should be taken into account in the management of chronic pancreatitis pain. However, how chronic nociceptive input leads to altered pain processing, how this is influenced by current therapies and how this may impact treatment success is largely unknown. Visualizing and measuring changes in pain processing clearly has the potential to provide us with exciting new insights for diagnosis and treatment.

A mechanism-orientated approach to chronic pain

To optimize diagnostics and treatment in chronic pain disorders a few key questions need to be answered:[40]

1) What is the source of nociception?
2) Is nociceptive transmission altered?
3) Is central pain processing altered?
4) Is altered central pain processing still dependent on peripheral nociceptive drive?

Suitable tools to answer these questions are i.e. quantitative sensory testing (QST), electroencephalography (EEG) and (functional) magnetic resonance imaging ((f)MRI). These three techniques have been used to describe changes in structure and function of the central nervous system in chronic pain disorders:

1) QST quantifies a test stimulus (i.e. pressure, electric or heat) and the patient's response to this stimulus (i.e. pain). The stimulus is applied to an anatomical site and increased until the subject reaches a predefined sensory threshold (i.e. sensation, pain or pain tolerance). Descending pain modulation can be measured using the conditioned pain modulation paradigm. In this paradigm a test stimulus is applied, followed by a conditioning stimulus and then again the test stimulus.[34,41] The difference between both test stimuli signals the size of descending modulation. By using different stimuli at different sites the subjects' state of pain processing can be characterized.

QST has been applied in all different kinds of chronic pain disorders showing similarities in pain mechanisms and physiology i.e. hypersensitivity to stimuli near and distant to the area of tissue damage as a sign of segmental and generalized hyperalgesia (changes in central pain processing).

2) Recording of electrical brain activity by EEG can also be used to study chronic pain disorders.[42] Two modalities are used in EEG: resting state (static element) and brain activity due to external stimuli reflected by evoked potentials (dynamic element). Alterations in the brain resting state have been observed in various chronic pain disorders. These alterations can be related to pain experience, however a direct correlation between pain intensity and alterations in the brain resting state is absent. Pain evoked studies in chronic pain disorders demonstrated alterations in dynamic pain processing after stimulation. Both support the presence of alterations in central nervous system processing in chronic pain disorders.

3) (f)MRI can be used to describe structural changes in the brain and changes in brain activity.[43,44] A variety of different techniques have been used in (f)MRI to analyze the central nervous system in chronic pain disorders and have shown changes in brain activity and structure in areas related to pain processing.

REASON FOR THIS THESIS

Our research group has a wide experience in research on pain processing and chronic pancreatitis.[34,35,45-48] Our research underlying the present thesis was mainly aimed at chronic pancreatitis patients who had chronic pain that is difficult to treat, even after successful invasive treatments targeting the source of nociception (i.e. pancreatic resections/drainage procedures, splanchnicectomy and endoscopic therapies).

One of our first studies was performed in chronic pancreatitis patients with intractable pain. We used bilateral thoracoscopic splanchnicectomy to denervate the pancreas and found early encouraging pain relief.[46] Long-term results of these patients showed that pain recurred in 50% of chronic pancreatitis patients, after four years this was 75%.[45,47] QST measurements in chronic pancreatitis patients before and after bilateral thoracoscopic splanchnicectomy showed an increase in pain thresholds, suggesting that bilateral thoracoscopic splanchnicectomy may reduce visceral nociceptive input.[35]

Overall QST, EEG and (f)MRI can be useful diagnostics to analyze central pain processing and optimize treatment in chronic pancreatitis. However, many questions need to be answered to achieve an optimal mechanism-orientated approach to chronic pain i.e. how does pain processing change during disease progression and how is this influenced by our therapies? Based on changes in pain processing can we provide new treatment strategies?

The main goal of this thesis is to describe the central pain mechanisms underlying chronic pain in chronic pancreatitis and to provide new insights regarding pain treatment in chronic pancreatitis.

AIMS OF THIS THESIS

1. To document and thus diagnose changes in central pain processing (central sensitization) in chronic pancreatitis, based on:
   a. The role of QST
   b. The role of (f)MRI
   c. The role of EEG

2. To evaluate the relationship between prognostic factors and central pain processing:
   a. The role of disease stage and progression
   b. The role of previous surgical interventions

3. To evaluate pain management in chronic pancreatitis and its relation to altered central pain processing:
   a. The effect of pancreatic surgery on pain processing
   b. The effect of medication active in the central nervous system
   c. The indication for medication active in the central nervous system

4. To propose a new, holistic view on pain management in chronic pancreatitis based on specific alterations in central pain processing present in the individual patient (therapeutic tailoring).

OUTLINE OF THE THESIS

The above-mentioned four aims have been elaborated in a clinical trial with several clinical and experimental endpoints, retrospective analyses, a clinical experiment and a review, which are presented in the subsequent chapters of this thesis.

Changes in central pain processing; central sensitization

Chapter 2 addresses abnormal brain function in painful chronic pancreatitis patients. Analysis of brain morphology using a 3T magnetic resonance scanner is used to compare cortical thickness (as a sign of structural reorganization) of brain areas involved in pain processing between healthy controls and chronic pancreatitis patients as a reflection of pain system dysfunction. It was shown that chronic pancreatitis patients have reduced

cortical thickness of brain areas involved in pain processing.
In **chapter 3** disease stage or progression is introduced, based on the M-ANNHEIM severity index of chronic pancreatitis, as a possible contributor to the extent of changes in central pain processing in chronic pancreatitis based on measurements by QST. Results suggested that changes in central sensitization may be influenced by disease stage. These findings suggest that altered central pain processing (i.e. degree of central sensitization) should be taken into account for pain management in chronic pancreatitis.
Chapter 4 addresses the question whether chronic pancreatitis patients after pain-relieving pancreatic surgery exhibit altered central pain processing compared to a healthy population measured by QST. Measurements showed that chronic pancreatitis patients exhibit altered central pain processing compared with healthy controls and that poor postoperative pain outcomes are associated with more central sensitization. These results suggest that in some painful chronic pancreatitis patients central sensitization is present, even when the nociceptive source (the pancreas) is adequately treated by pancreatic drainage and/or resection procedure (i.e. central autonomy of pain).
Altered pain processing that is independent of ongoing peripheral nociceptive input was further studied in **chapter 5**. This phenomenon was tested by performing QST in chronic pancreatitis patients who had undergone bilateral thoracoscopic splanchnicectomy for central sensitization and then studying its relation to pain relief. A subgroup of patients showed no postoperative pain reduction linked to no reduction in central sensitization suggesting an autonomous pain state independent of peripheral nociceptive input.

When central sensitization is present, can we treat it?
In **chapter 6** we describe the effects of S-ketamine (NMDA receptor antagonist) and placebo infusion on pain relief and pain thresholds, as a sign of central sensitization, in chronic pancreatitis patients. It is shown that S-ketamine infusion is more effective in increasing pain thresholds then placebo, although the effect did not outlast infusion duration.
The results of a randomized controlled trial which compares pregabalin (gabapentinoid) and placebo and its effect on pain in chronic pancreatitis patients are described in **chapter 7**. Study results showed that pregabalin is an effective adjuvant in pain treatment for chronic pancreatitis patients.
The experimental endpoints of the randomized controlled trial comparing pregabalin and placebo in chronic pancreatitis are reported and discussed in **chapter 8**. QST was used to evaluate the effect of pregabalin on pain processing in chronic pancreatitis and showed that pregabalin has moderate inhibitory effects on central sensitization. Evidence for QST as a monitoring strategy for pain treatment was also provided.
Other experimental endpoints of the randomized controlled trial are analyzed in

chapter 9. QST was used to investigate differences in pain sensitivity and modulation in chronic pancreatitis among responders and non-responders to placebo or pregabalin treatment. The results showed that there is a potent placebo effect in chronic pancreatitis patients. Antihyperalgesic effects are seen in chronic pancreatitis patients responding to pregabalin, but not in those responding to placebo. The observed antihyperalgesic effect affected both ascending and descending pathways.

A new holistic view on pain management in chronic pancreatitis

A systematic mechanism-orientated approach to pain in chronic pancreatitis is presented in chapter 10 as a general discussion of this thesis together with future perspectives. This approach is based on the finding that chronic pancreatitis shows similarities with other chronic pain disorders and should be managed in a similar fashion. In some patients ongoing pain may induce altered central pain processing. Suitable tools to visualize altered central pain processing are QST, EEG and (f)MRI and should be used to optimize treatment strategies in chronic pancreatitis receiving, e.g. central active medication.

Most studies in this thesis focus on changes in pain processing in chronic pancreatitis after interventions e.g. denervation procedures and resections or drainage procedures, and during disease progression. The other studies describe the clinical effect of centrally active medication on chronic pain and how medication changes central pain processing. All these studies taken together, together with the present literature on chronic pain management in visceral pain syndromes, formed the basis for the review in our last chapter (general discussion and future perspectives).

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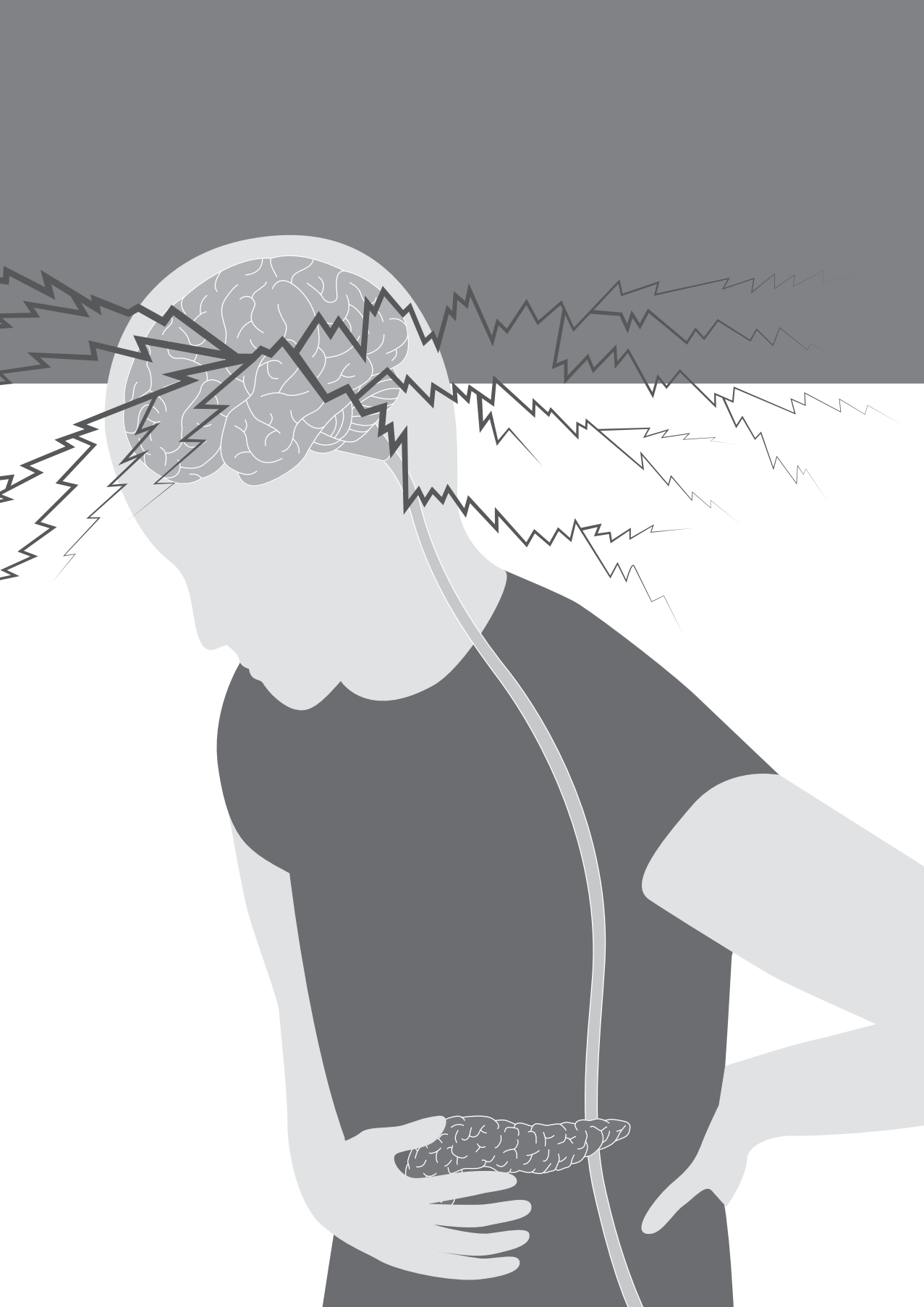

Chapter 2

Reduced cortical thickness of brain areas involved in pain processing in patients with chronic pancreatitis

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ABSTRACT

Background & aims

Patients with painful chronic pancreatitis might have abnormal brain function. We assessed cortical thickness in brain areas involved in visceral pain processing.

Methods

We analyzed brain morphologies of nineteen patients with painful chronic pancreatitis and compared them with fifteen healthy individuals 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 one week.

Results

Compared with controls, patients with chronic pancreatitis had reduced overall cortical thickness ($P = 0.0012$), without effects of modification for diabetes, alcoholic etiology, or opioid treatment (all P values > 0.05). In patients with chronic pancreatitis, the cortical thickness was decreased when compared with controls in SII ($P = 0.002$), PFC ($P = 0.046$), FC ($P = 0.0003$), MCC ($P = 0.001$), and insula ($P = 0.002$). There were no differences in cortical thickness between chronic pancreatitis patients and controls in the control area ($P = 0.20$), SI ($P = 0.06$), ACC ($P = 0.95$), or PCC ($P = 0.42$). Cortical thickness in the affected areas correlated with pain score ($r = 0.47$, $P = 0.003$).

Conclusions

In patients with chronic pancreatitis, 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 also seen in other diseases characterized by chronic pain.

INTRODUCTION

In a majority of patients with chronic pancreatitis, 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 chronic pancreatitis 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 chronic pancreatitis has been ascribed to the diseased pancreas itself, i.e. ongoing inflammation, pseudocyst formation and ductal abnormalities with increased ductal and parenchymal pressure.[2] However, in many of these patients, there is histological 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.[10] However, the exact mechanisms behind both 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 chronic pancreatitis patients.

We hypothesized that chronic pancreatitis 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 chronic pancreatitis patients; and 2) to correlate the findings in patients with the clinical pain data.

METHODS

Subjects

Nineteen patients with chronic pancreatitis from the department of Gastroenterology and Hepatology, Aalborg Hospital were included. The diagnosis of chronic pancreatitis was based on the Mayo Clinic diagnostic criteria.[18] The inclusion criteria were abdominal pain typical for pancreatitis (i.e. dull epigastric pain, eventually radiating to the back) and

chronic pain (i.e. pain ≥ three days per week for at least three months). Both patients on stable opioid medication and patients on non-opioid analgesics were included. Patients with other acute or chronic pain syndromes (e.g. 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 - 10 visual analogue scale) with assessment of daily average pain for one week prior to 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 based on high-resolution 3D MRI (Figure 1), including average data for the entire hemispheres and individual anatomical regions of interest (ROIs) according to the Montreal Neurological Institute system.[19] The method is described in supplementary material.

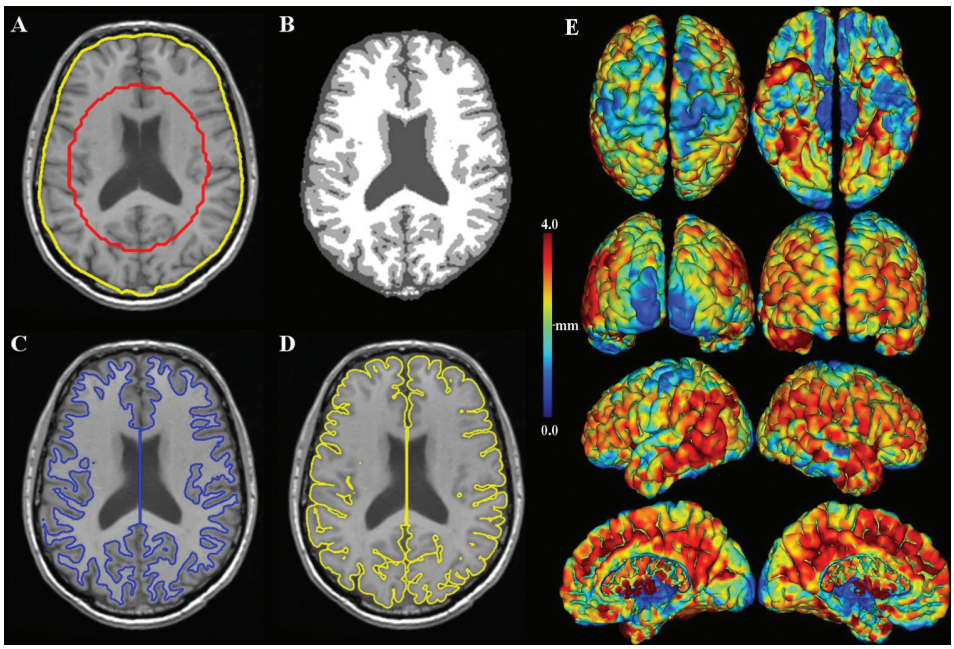
The ROIs included in the present study were hypothesis-driven on the basis of previous studies and the knowledge of the processing of visceral pain[10,12,13,20]: 1) primary somatosensory cortex (SI) defined as the postcentral gyrus; 2) secondary somatosensory cortex (SII) defined as the Rolandic operculum; 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), posterior (PCC) divisions of the cingulate cortex; 6) insula defined as the entire insula, and as control area; and 7) occipital middle sulcus.

Statistics

All results are expressed as means with standard deviations. Differences in age, gender distribution, and structural MRI findings were analyzed using Student's t-test or Fisher's exact test as appropriate. The differences in cortical thickness between chronic pancreatitis patients and controls were compared by a three-step procedure. First, the overall differences in cortical thickness were compared by Student's t-test. The retrieved differences were further adjusted in a sub-analysis (two-way analysis of variance (ANOVA)), with stratification for opioid treatment, diabetes mellitus, alcohol etiology, and pain pattern (continuous vs. attack-wise) of chronic pancreatitis. 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 (chronic pancreatitis 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 as it limits the likelihood of type II errors, which would result in truly important differences being deemed non-significant.[21] Normality was checked by Q-Q plots and the assumption of variance homogeneity by Levene's test. Correlations between cortical thickness values and clinical parameters (Table 1) and between the dose of analgesics (morphine equivalents per day) and pain intensity were analyzed using the Pearson correlation coefficient. $P < 0.05$ were considered significant. The software package Stata version 11.2 (StataCorp LP, College Station, TX, USA) was used for the statistical analysis.

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 the MRI data. E) The cortical thickness distribution of a healthy subject is shown.

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 $P > 0.05$). Two patients had previous surgery with partial pancreatic resections. All control subjects

had a normal structural MRI of the brain, whereas three patients had evidence of diffuse cortical atrophy (two minor and one moderate), and six patients had minor white matter lesions (both P > 0.05 compared with controls). No other pathological findings were seen. None of the lesions were located in or near the ROIs.

TABLE 1
Demographic and clinical characteristics of patients and healthy volunteers

	Chronic pancreatitis (N = 19)	Healthy volunteers (N = 15)
Age – years (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 (VAS, 0 – 10)		
Average pain	3.6 ± 2.0	
Morphine equivalents/day – mg (range)	53 (0 – 210)	
Duration of chronic pancreatitis – months	95 ± 45	
Diabetes mellitus – no. (%)	6 (32)	0 (0)

Data are means with standard deviations when not mentioned otherwise. 'VAS' means visual analogue scale. [a]According to the TIGAR-O classification system.[39]

Overall cortical thickness

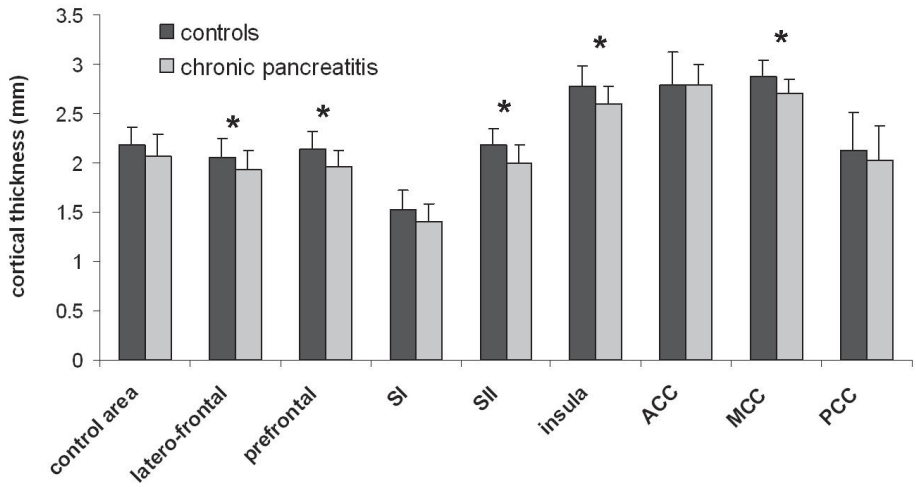
In chronic pancreatitis patients the overall cortical thickness including the entire brain hemispheres was 1.98 ± 0.11 mm, compared with 2.11 ± 0.10 mm in the control group (P = 0.0012). No effect modification on the overall cortical thickness was seen from alcoholic etiology of chronic pancreatitis (F = 0.01, P = 0.92), the presence of diabetes mellitus (F = 1.61, P = 0.21), opioid treatment (F = 0.97, P = 0.33), or pain pattern (continuous vs. attack-wise) (F = 0.18, P = 0.67).

Cortical thickness in predefined pain-related regions of interest

Compared with controls, chronic pancreatitis patients had decreased cortical thickness in 1) SII (F = 11, P = 0.002), with right side thicker than the left (F = 18, P = 0.0002); 2)

PFC (F = 4.3, P = 0.046), with no side difference (F = 0.11, P = 0.74); 3) FC (F = 16, P = 0.0003), with no side difference (F = 0.06, P = 0.80); 4) MCC (F = 13, P = 0.001), with no side difference (F = 0.49, P = 0.49); and 5) insula (F = 12, P = 0.002), with right side thicker than the left (F = 20, P = 0.0001) (Figure 2).

FIGURE 2



Mean cortical thickness (average of left and right sides) of the control area and pain-related areas in patients with painful chronic pancreatitis and in healthy subjects.
Values are means with standard deviations. Error bars are standard deviation. 'SI' is primary, 'SII' secondary somatosensory cortex, 'ACC' anterior cingulate cortex, 'MCC' is mid cingulate cortex and 'PCC' posterior cingulate cortex. *: $P < 0.05$.

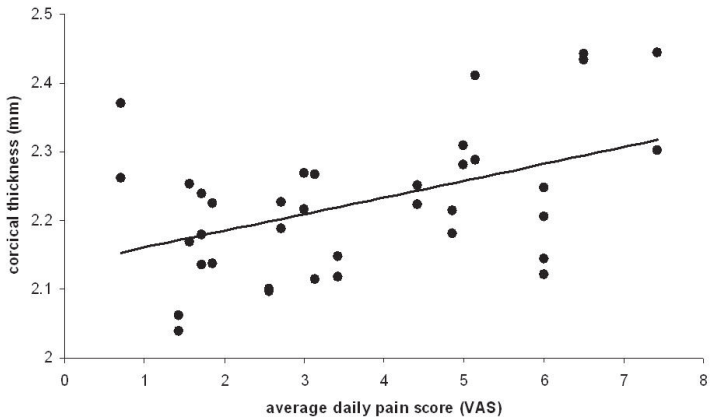
No difference in cortical thickness between chronic pancreatitis patients and controls was seen in 1) SI (F = 3.8, P = 0.06), with no side difference (F = 3.3, P = 0.57); 2) ACC (F < 0.01, P = 0.95), with left side thicker than the right (F = 7.5, P = 0.01); and 3) PCC (F = 0.68, P = 0.42), with left side thicker than the right (F = 15, P = 0.0004).
In the control area (occipital middle sulcus) no difference in mean cortical thickness was seen between chronic pancreatitis patients and controls (F = 1.69, P = 0.20), but right side was thicker than left (F = 68, P < 0.0001).

Correlation with clinical scores

The mean cortical thickness of all five ROIs showing a difference between chronic pancreatitis and controls (SII, PFC, FC, MCC and insula) was considered for correlation analysis. A positive correlation was seen between cortical thickness and diary pain score

(r = 0.47, P = 0.003) (Figure 3). A borderline significant negative correlation was seen between cortical thickness and the duration of chronic pancreatitis (r = -0.31, P = 0.06). No correlation was seen between cortical thickness and age (r = -0.16, P = 0.35) or dose of analgesics (r = 0.06, P = 0.64). A positive correlation was seen between the dose of analgesics and diary pain score (r = 0.48, P = 0.03).

FIGURE 3



Correlation between the average daily pain score assessed on a 0 – 10 visual analogue scale (VAS) and the cortical thickness (including the mean of the: secondary somatosensory, prefrontal, frontal and mid cingulate cortex, and insula for left and right sides separately).

DISCUSSION

In patients with painful chronic pancreatitis we found reduced cortical thickness in brain areas known to be involved in the processing of visceral pain. In contrast, no difference in cortical thickness was seen in the occipital control area. The cortical thinning found in these areas was correlated to the patients' clinical pain score. Together with the absent effect modifications from comorbidities or previous alcohol abuse, this supports the meaningfulness of the results and suggests that the findings are related to the patients' pain, with ongoing pain resulting in structural reorganization of the neuromatrix expressed as regional differences in cortical thickness.

Methodological considerations

Cortical thickness analysis is fundamentally different from voxel-based morphometry, which assesses gray matter density, and which has already been used to study chronic

pain.[22] The method for cortical thickness analysis used in the present study (FACE) has proved to be fast, accurate and robust for segmenting the cortical boundaries, especially taking the problems with opposite banks of tight sulci into account.[15] In terms of accuracy, the FACE method is comparable or better (more than 25 times faster) than the FreeSurfer method[16], which has been used in studies of irritable bowel syndrome and trigeminal neuropathic pain.[12-14]

The selection of ROIs was hypothesis-driven on the basis of previous studies and the knowledge of the processing of visceral pain, i.e. the so-called pain matrix.[10,12,13,20] The PFC and ACC are central in the processing of visceral pain, and the PFC is involved in the cognitive aspects of the pain experience. The FC receives sensory inputs from SI, SII and insula, and is involved in the processing of reward including decision making[23], but also pain[24]. 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 the cingulate gyrus is mainly involved in the emotional, affective/cognitive response to pain.[25-31] In addition, the MCC is proposed to connect with hypothalamus and periaqueductal gray as a part of the descending pain modulation system.[32] The selection of ROIs is comparable to that in studies of irritable bowel syndrome and trigeminal neuropathic pain, including the identical occipital control area where there is little or no evidence of any significant role in neuropathic pain.[12-14]

Chronic pain depends on multiple factors of which many are difficult to quantify and control. The diary pain score used in the present study is validated in chronic pain studies and represents a robust measure of pain intensity.[33,34] It has previously been used in assessment of pain in chronic pancreatitis.[10,35] The pain scores were based on one-week reports and thus cannot represent the total pain intensity during several years. Unfortunately, no behavioral or psychological data of the pain experience were recorded, even though these parameters also are of great importance. However, most patients had a relative stable pain pattern and we therefore consider the one-week report representative for pain intensity over time. Furthermore, patients diagnosed with chronic pancreatitis often present with abdominal pain as their leading symptom. Consequently, the duration of pain corresponds roughly to the duration of chronic pancreatitis.

Pain processing in chronic pancreatitis

Previous neurophysiological studies of patients with painful chronic pancreatitis have found widespread visceral hypersensitivity with evidence for sensitization and cerebral reorganization.[6,7,11] Hence, the underlying electrical brain activity to gut stimulation in chronic pancreatitis patients showed that the insular and cingulate sources were abnormally localized, and this shift in source localization correlated with clinical pain scores.[5,35] The electrophysiological indication of functional reorganization of the cortex

was further supported in a recent study using magnetic resonance diffusion tensor imaging, where microstructural changes of white and gray matter in pain-related brain areas were found.[10]

The changes in cortical thickness seen in the present study further extend the evidence of changes in the pain matrix in painful chronic pancreatitis and are comparable with findings seen in irritable bowel syndrome and trigeminal neuropathic pain.[12-14] Although establishment of an exact correlation between functional, microstructural and cortical changes is difficult, the observed cortical changes correspond in a meaningful way to the neurophysiological and microstructural changes described above.

The MCC cortical thinning in the present study is consistent with findings in patients with irritable bowel syndrome.[12,36] The MCC functions together with the hypothalamus and periaqueductal gray as a part of the 'top-down' descending pain modulation system, where several supraspinal areas can directly or indirectly modulate the nociceptive processing in the spinal dorsal horn.[32] The finding of cortical thinning in the MCC may therefore represent a neuroanatomical correlate of an impaired function of endogenous pain inhibition, in agreement with a previous study from our group.[11]

The cortical thinning in PFC and FC in chronic pancreatitis corresponds to previous findings in trigeminal neuropathic pain and might reflect that these brain regions are involved in cognitive aspects of pain.[13] Apkarian et al found reduction in the volume of gray matter in the PFC and thalamus of patients with chronic back pain, with strong relation to pain characteristics (neuropathic vs. non-neuropathic).[37] The reduced frontal cortical thickness in chronic pancreatitis may reflect a neglect of pain input. Although speculative, the positive correlation between cortical thickness (including both PFC and FC) and chronic pancreatitis pain may relate to such compensatory pain inhibitory mechanisms.

The insular cortical thinning corresponds to the cortical thinning in patients with short-term irritable bowel syndrome.[12] The cortical changes in insula and SII, which are intensively functionally and anatomically connected, might thus correspond to the central position of these areas in the processing of chronic pancreatitis pain.[5,35]

The positive correlation between cortical thickness (including both SII and insula) and diary pain score parallels the positive correlation between anterior insula thickness and pain duration in irritable bowel syndrome and trigeminal neuropathic pain.[12,13] In contrast, most cortical thickness studies (typical chronic somatic pain, such as chronic back pain, post-herpes neuralgia and osteoarthritis) have revealed a negative correlation between cortical thickness and pain.[22] Even though data on the long-term use of analgesics were not available, the present dose of analgesics (morphine equivalents per day) did not correlate to cortical thickness indicating that previous use of analgesics per se cannot explain the positive correlation. This is further strengthened by the positive correlation between the dose of analgesics and pain intensity. However, the neuroplastic response

to prolonged pain input is likely complex, and the changes in neural architecture may result in a variety of microstructural and cortical thickness changes seen on MRI. Other factors such as behavioral and autonomic responses that can be negatively related to pain intensity were not controlled for. These may also influence brain activity and hence cortex thickness. In line with our findings, Fregni et al[38] reported an over-activated SII in chronic visceral pain with pain relief after application of transcranial magnetic stimulation to this area and increased level of SII glutamate in chronic pancreatitis patients using magnetic resonance spectroscopy. Even though the pain pattern is known to influence the brain microstructure in chronic pancreatitis[10], no effect modification from the pain pattern was seen in the present study.

The demonstrated cortical changes in painful chronic pancreatitis could be a result of neuroplasticity induced by sustained chronic pain and of increased synaptic activity in the brains pain matrix related to the greater inhibitory activity generated to counterbalance the nociceptive input. However, it cannot be excluded that secondary structural brain alterations induced by comorbidities influence cortical thickness. This cannot be definitively answered as the study lacked a matched control group of chronic pancreatitis patients without abdominal pain. Such patients are very difficult to find as they typically have less severe disease. On the other hand, there was no influence from comorbidities (excessive alcohol consumption, diabetes or opioid therapy), and there was a trend towards correlation between cortical thickness of pain-specific areas and the duration of chronic pancreatitis. Findings from other chronic pain conditions parallel our findings. We therefore consider chronic abdominal pain likely to be the most important drive of the demonstrated cortical abnormalities.

Conclusion

Patients with painful chronic pancreatitis have decreased cortical thickness of brain areas involved in visceral pain processing. These alterations seem to have functional significance and support the existing body of knowledge from neurophysiologic and microstructural studies. As the end result of longstanding ongoing pain input to the neuromatrix, cortical thickness might serve as a valid measure of the overall damage and dysfunction of the pain system. These findings might contribute to our understanding of the pathophysiology underlying pain in chronic pancreatitis.

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SUPPLEMENTARY MATERIAL

Cortical thickness analysis

All subjects were investigated at Aalborg Hospital on a 3T MRI scanner (Signa HDxt; General Electric, Milwaukee, WI) equipped with an 8-channel standard head coil. Axial T2-weighted fluid attenuated inversion recovery (FLAIR)-sequence images (field of view, 25 x 25 cm; matrix 352 x 224; 5 mm slice thickness; whole brain coverage; repetition time 8802 ms; echo time 127 ms; inversion time 2200 ms) were evaluated for atrophy, white matter lesions and other pathology. Axial T1-weighted 3D brain volume imaging (BRAVO)-sequence images (field of view, 25x25 cm; 320x320 matrix; 1.0 mm slice thickness; full head coverage; flip angle 14°; repetition time 9.0 ms; echo time 3.6 ms) were obtained for the cortical thickness analysis. All images were checked for obvious motion and susceptibility artifacts that could affect the image processing and subsequent quantification.

The method consisted of the following completely automated steps. The 3D MRI data were registered to the ICBM152 model by using an automatic iterative multiresolution approach.[1,2] Intensity non-uniformities were corrected by the N3 algorithm,[3] and a brain mask was created using an algorithm similar to the brain extraction tool by Smith.[4] The voxels inside the brain mask were classified into white matter, grey matter and cerebrospinal fluid using a fuzzy clustering algorithm. Topologically correct surfaces of the white matter were generated from the white matter classification. These surfaces were iteratively deformed to respectively the white/gray matter and gray matter/cerebrospinal fluid boundary of the cortex. The cortical thickness was calculated as the distance between the white/gray matter boundary and the gray matter/cerebrospinal fluid boundary perpendicular to the cortical surface. Thickness calculations were performed in scanner space to avoid a bias toward the model. Each cortical surface was geometrically smoothed and mapped to a reference surface in standard space by using a feature-driven surface mapping algorithm.[5,6] The reference surface is divided into anatomical regions by using the definition by Tzourio-Mazoyer et al.[7] Cortical thickness measurements were averaged within these regions.

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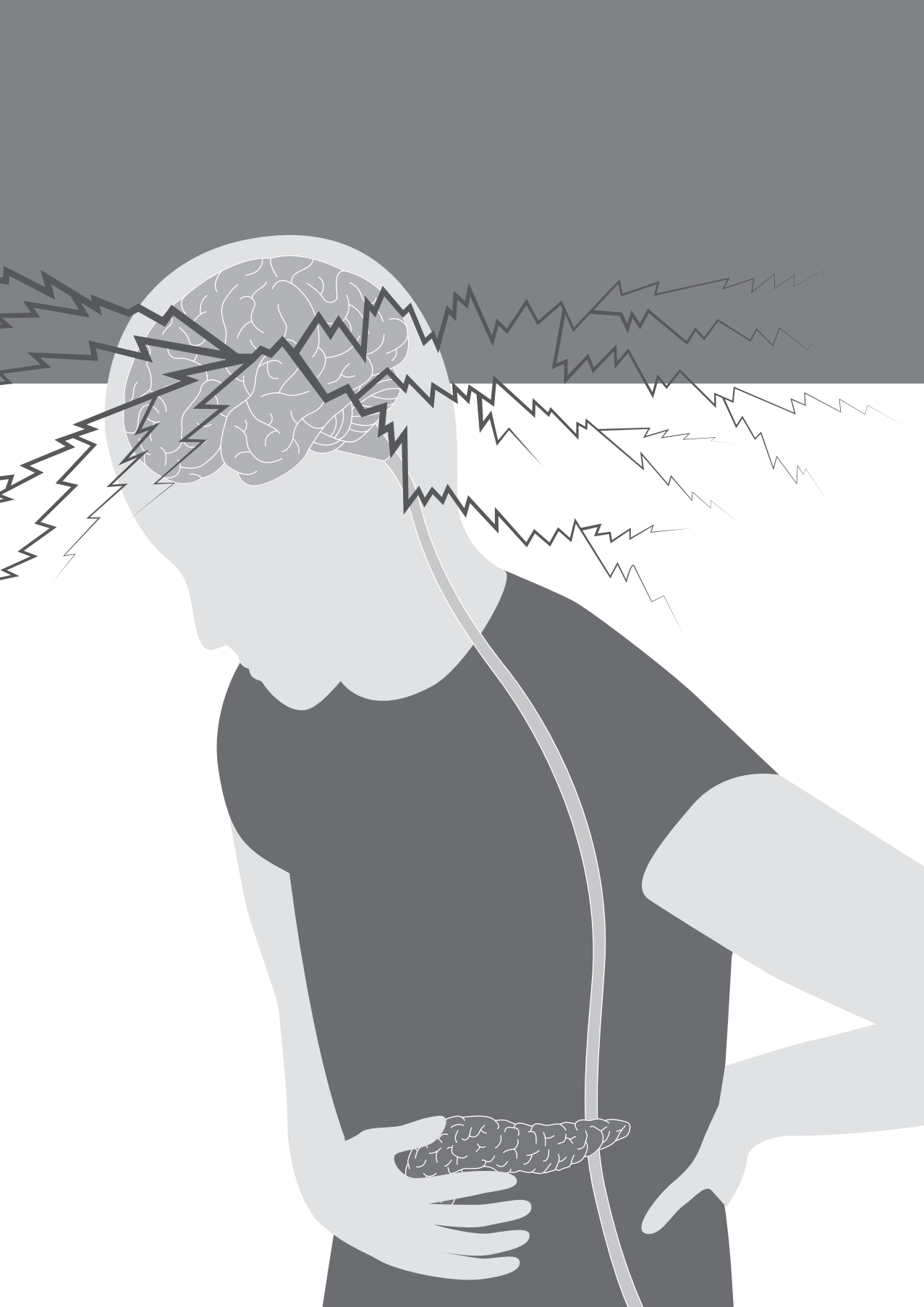

Chapter 3

Is altered central pain processing related to disease stage in chronic pancreatitis patients with pain? An exploratory study

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ABSTRACT

Background

The most dominant feature in chronic pancreatitis is intense abdominal pain. Changes in spinal and/or supraspinal central nervous system pain processing due to visceral nociceptive input play an important role in this pain. How altered pain processing is related to disease stage still needs study.

Methodology/principal findings

Sixty chronic pancreatitis patients were compared to fifteen healthy controls. Two subgroups of pancreatitis patients were defined based on the M-ANNHEIM severity index of chronic pancreatitis; i.e. moderate and severe. Pain detection and tolerance thresholds for pressure and electric stimuli were measured in six selected dermatomes (C5, T4, T10, L1, L4 and T10 BACK (dorsal)). In addition, the conditioned pain modulation response to cold pressor task was determined. These measures were compared between the healthy controls and chronic pancreatitis patients. Severe pancreatitis patients showed lower pain thresholds than moderate pancreatitis patients or healthy volunteers. Healthy controls showed a significantly larger conditioned pain modulation response compared to all chronic pancreatitis patients taken together.

Conclusions/significance

The present study confirms that chronic pancreatitis patients show signs of altered central processing of nociception compared to healthy controls. The study further suggests that these changes, i.e. central sensitization, may be influenced by disease stage. These findings underline the need to take altered central pain processing into account when managing the pain of chronic pancreatitis.

INTRODUCTION

Intense upper abdominal pain is common in chronic pancreatitis patients and is the most important predictor of health-related quality of life.[1,2] The etiology of pain remains to be elucidated and no generally accepted guidelines exist for its treatment. Initial treatment typically consists of a low fat diet and non-narcotic analgesics.[2] Alternatives to medical treatment, for example pancreatic surgery, thoracoscopic splanchnicectomy and lithotripsy, may have an effect on pain in selected patients.[3-5] If no acceptable pain relief is obtained, opioids remain the mainstay for the management of pain. However, opioids have many adverse effects such as negative influence on gastrointestinal motility, central nervous system toxicity, addiction and abuse potential, and sometimes opioid-induced hyperalgesia.[6] Thus, new treatment regimes for the debilitating pain of chronic pancreatitis are still needed. Adjuvant therapy with, e.g. pregabalin has recently been proven to be effective in chronic pancreatitis.[7,8] However, centrally acting agents i.e. gabapentinoids or tricyclic antidepressants are not yet an accepted part of pain treatment in chronic pancreatitis.

Answering questions like "How do chronic pancreatitis patients process pain and how does altered pain processing relate to their pain experience?" is fundamental for the design of new therapeutic strategies. In human experimental pain models basic pain mechanisms can be explored by quantitative sensory testing (QST), electroencephalography (EEG) or magnetic resonance imaging (MRI).[9-12] These techniques provide insight into various aspects of pain processing during progression of a painful disease, as well as before and after a therapeutic intervention.[13]

QST is increasingly used to study pain mechanisms in painful conditions.[13-16] A key described alteration in chronic pancreatitis patients is segmental and generalized hyperalgesia, often present despite (or because of) opioid usage.[9,17] These changes are similar to those seen in neuropathic pain syndromes.[11] Their presence suggests that increased sensitivity in the central nervous system at spinal and/or supraspinal sites (central sensitization) plays an important role in chronic pancreatitis pain, and that this is not effectively modulated by current opioid-based therapies.[11] Conditioned pain modulation (CPM) is a dynamic QST paradigm designed to activate and measure pain modulating mechanisms, e.g. via descending inhibitory control where brain stem centers act on nociceptive neurons in the dorsal horn of the spinal cord.[18] An impaired CPM response has been reported in chronic pancreatitis as well as in other gastrointestinal diseases and neuropathic conditions exhibiting hyperalgesia.[19-21]

At present, comprehensive comparisons between chronic pancreatitis patients at different disease stages and compared with a healthy population regarding pain processing are not available. Such observations related to disease progression may also be of clinical value for other chronic painful disorders e.g. ulcerative colitis and Crohn's disease.[22]

The objective of this study is to investigate the difference in pain sensitivity and

modulation between healthy subjects and chronic pancreatitis patients using QST to determine: 1) pressure pain thresholds; 2) electric pain thresholds; and 3) CPM response. Our hypothesis is that pain in chronic pancreatitis is accompanied by alterations in pain processing, and that this is influenced by disease stage.

METHODS

Study patients

The study was approved by the responsible Ethical Committees in both countries (CMO region Arnhem-Nijmegen, Nijmegen, the Netherlands and The local Ethics Committee North Region, Aalborg, Denmark) and all patients provided written informed consent. Patients were recruited for an investigator initiated double-blind, placebo-controlled, parallel-group study of increasing doses of pregabalin conducted in the Netherlands (department of Surgery, Radboud university nijmegen medical center) and Denmark (department of Gastroenterology, Aalborg Hospital, Aarhus University Hospital). The study was powered on a clinical primary outcome measure which is presented in another manuscript and not on the QST measurements that are described in this manuscript. The present study only presents the baseline QST results of all the 64 patients that were included in this trial.[7]
To be included in this study, patients needed to have chronic abdominal pain typical for pancreatitis (i.e. dull epigastric pain more than three days per week for at least three months) and a diagnosis of chronic pancreatitis based on the Mayo Clinic diagnostic criteria.[23] Patients were excluded from the study if they had a painful condition other than chronic pancreatitis, an active (or history of) major depression, severe renal impairment, an abnormal electrocardiogram at screening, allergy to pregabalin or any of it components and were pregnant or lactating.

Healthy controls

A healthy control group was recruited in Denmark for comparison with our chronic pancreatitis group. The controls did not have any active disease and no history of a medical condition that could interfere with our pain measurements. Measurements were performed in females in the same phase of the menstrual cycle. Informed consent was provided by all healthy controls.

Quantitative sensory testing

QST took place using a standard temporal test sequence.[9] Testing in females with pancreatitis was not standardized with regard to phase of the menstrual cycle because all female pancreatitis patients had amenorrhoea or were postmenopausal. After initial QST training, pressure pain thresholds were obtained for muscles overlying bone using

a pressure algometer with a 1.0 cm^2 probe (Somedic Sales AB, Horby, Sweden), at each of the following sites on the dominant body side: lower neck (C5 dermatome), sternum (T4 dermatome), pancreatic site (T10 BACK (dorsal) dermatome) and ventral (T10 dermatome), hip region (L1 dermatome) and knee (L4 dermatome).
The pancreatic and more distant dermatomes were chosen to permit observation of segmental and spreading hyperalgesia respectively. The upper abdominal area (T10 ventral and dorsal) was chosen to detect segmental hyperalgesia because dorsal horn neurons receiving painful stimuli from this skin area also receive nociceptive stimuli from the pancreas (i.e. pancreatic area). To examine spreading and generalized hyperalgesia we chose two dermatomes (proximal and dorsal) near the pancreatic area (dermatomes T4 and L1) and two dermatomes more distant (proximal and dorsal) from the pancreatic area (dermatomes C5 and L4). The more distant areas were chosen to act as a control area likely unaffected by pancreatic nociceptive input because the nociceptive pathways from these areas are well separated from those coming from the pancreas at both peripheral and spinal levels.
Two thresholds were measured: pressure pain detection threshold (pPDT) and pressure pain tolerance threshold (pPTT).
Thresholds to electric constant current skin stimulation (Digistim; Biometer A/S, Copenhagen, Denmark; tetanic stimulation at 100 Hz, 0.2 ms square waves, self-adhesive electrodes 3 cm apart) were measured on the same sites as for pressure stimulation. Two thresholds were measured: electric pain detection threshold (ePDT) and electric pain tolerance threshold (ePTT).
The conditioned pain modulation (CPM, previously known as diffuse noxious inhibitory control (DNIC)) paradigm was carried out to test the ability of the patient to generate descending inhibitory modulation.[24,25] Thus pressure pain tolerance thresholds (pPTT, the test stimulus) were determined before and after the cold pressor task (the conditioning stimulus), and the CPM effect was determined as the relative change (%) in pPTT. For the cold pressor task the dominant hand was immersed in ice-chilled water (1.0 °C ± 0.3 °C) continuously stirred by a pump. The patient was told to remove the hand from the water after two minutes of immersion - or sooner if the pain was considered to be intolerable – and the immersion time noted. Immediately after the cold pressor task, the subjects rated the pain experienced during the test by use of a visual analogue scale for quality control purposes. pPTT were obtained in the non-dominant L4 dermatome (knee) immediately before and after ice water immersion.

Disease stage

We formed two groups of patients based on 'the M-ANNHEIM severity index of chronic pancreatitis' which is a validated clinical disease stage classification for chronic

pancreatitis.[26] The M-ANNHEIM classification system incorporates etiology, different stages of the disease, and various degrees of clinical severity. The M-ANNHEIM scoring system for a clinical severity index is a simple, accurate and noninvasive tool in clinical practice and may be helpful in investigating the impact and interaction of various risk factors on the course of the disease. Clinical severity is based on pain control, surgical interventions, pancreatic endocrine and exocrine insufficiency, morphological status and severe organ complications.
We divided the patients in two groups based on their score, namely: ≤ ten points, moderate chronic pancreatitis group (including: minor and increased severity level) and > ten points, severe chronic pancreatitis group (including: advanced and marked severity level).

Statistical analysis

The study was powered to detect a difference in average daily pain scores of 25% between groups during the three weeks of study treatment. We determined that a study with 30 patients per group was needed to provide a power of 90% with the use of a two-sided significance level of 0.05. Hence, the sample size was set at 64 patients to allow for possible dropouts.
We performed statistical analysis using the Statistica for Windows Software Package (Release 6.0, Statsoft Inc., Tulsa, OK, USA). All results are given as means with standard deviations or 95% confidence intervals as appropriate. We analyzed QST results using a mixed model two-way ANOVA with one between subjects factor (GROUP; i.e. a healthy control group and two chronic pancreatitis groups according to disease stage) and one within subjects factor (SITE; consisting of the six dermatomes mentioned under quantitative sensory testing). We analyzed CPM results using a one-way ANOVA with one between subjects factors (GROUP; as above). Post hoc analysis was performed using Fisher's exact test.

RESULTS

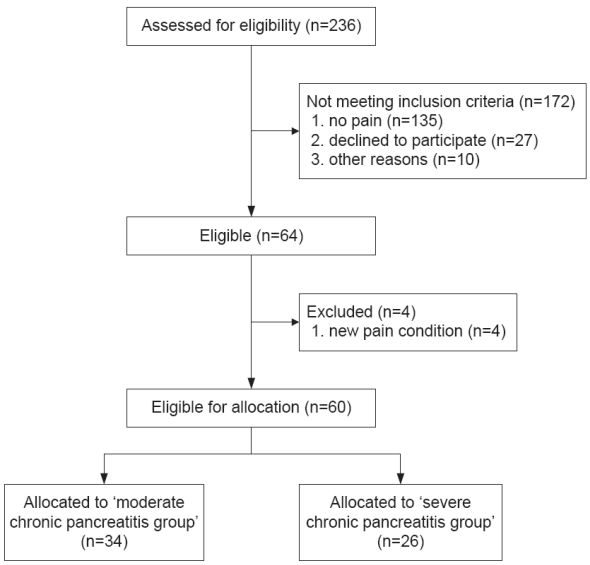
Study population

From October 2008 to May 2010 a total of 236 patients diagnosed with chronic pancreatitis in the last five years in one of both hospitals were screened and 64 patients were randomized; the study was completed without any incident. The majority of patients not meeting inclusion criteria were pain free, had passed away or were no longer being treated in either of the hospitals. From those 64 patients, four patients were excluded due to a new pain condition (e.g. complication of chronic pancreatitis requiring surgery, tooth abscess, emergency vascular surgery and diagnosis of inflammatory bowel disease) that would interfere with their QST measurements (Figure 1). All patients in this

per-protocol analysis (24 women, 36 men; mean age 54 ± 11) had pain due to chronic pancreatitis and were on a stable analgesic therapy. The healthy control group consisted of fifteen volunteers. The moderate chronic pancreatitis group consisted of 34 patients and the severe group of 26 patients (Table 1). Pancreatitis groups were statistically comparable except – as expected – for previous interventions. More demographic data on the study population and control group are listed in Table 2.

FIGURE 1

Study enrollment and randomization



The majority of patients 'not meeting inclusion criteria' had either died, was pain free or was no longer being treated in either of the hospitals.

TABLE 1

M-ANNHEIM severity index of chronic pancreatitis and distribution of patients

	Severity level	Point range	Frequency no. (%)
M-ANNHEIM A	Minor	0 – 5	4 (7)
M-ANNHEIM B	Increased	6 – 10	30 (50)
M-ANNHEIM C	Advanced	11 – 15	21 (35)
M-ANNHEIM D	Marked	16 – 20	4 (7)
M-ANNHEIM E	Exacerbated	> 20	1 (2)

M-ANNHEIM scoring system points are added together, and the sum is used to categorize a patient's disease according to the M-ANNHEIM severity index.

TABLE 2

Demographic and clinical characteristics of patients and healthy controls

	Healthy controls (N = 15)	Moderate chronic pancreatitis group (N = 34)	Severe chronic pancreatitis group (N = 26)
Age (years)	40 ± 9*	53 ± 11	53 ± 11
Males - no. (%)	8 (53)	24 (71)	12 (46)
Etiology - no. (%)			
Toxic-metabolic	0	17 (50)	13 (50)
Idiopathic	0	13 (38)	8 (31)
Genetic	0	1 (3)	1 (4)
Autoimmune	0	0	1 (4)
Recurrent and severe acute pancreatitis	0	2 (6)	1 (4)
Obstructive	0	1 (3)	2 (8)
Diary pain score (numeric rating score, 0 - 10)			
Average pain	0	4 ± 2	4 ± 2
Maximal pain	0	5 ± 2	6 ± 2
Concomitant analgesics - no. (%)†			
None	0	4 (12)	1 (4)
Weak analgesics	0	7 (21)	10 (39)
Strong analgesics	0	23 (68)	15 (58)
MEQ/day (mg)	0	112 ± 132	72 ± 71
Antidepressants - no. (%)	0	6 (18)	6 (23)
Duration of chronic pancreatitis (months)	0	113 ± 85	100 ± 75
Diabetes mellitus - no. (%)	0	4 (12)	14 (54)*
Previous interventions for chronic pancreatitis - no. (%)	0	2 (6)	13 (50)*
Pancreas resection / drainage procedures	0	2 (6)	8 (31)*
Thoracoscopic splanchnic denervation	0	1 (3)	7 (27)*
Celiac blockade	0	0	2 (8)*
Patients treated with enzymes for pancreatic exocrine insufficiency - no. (%)	0	11 (32)	17 (65)

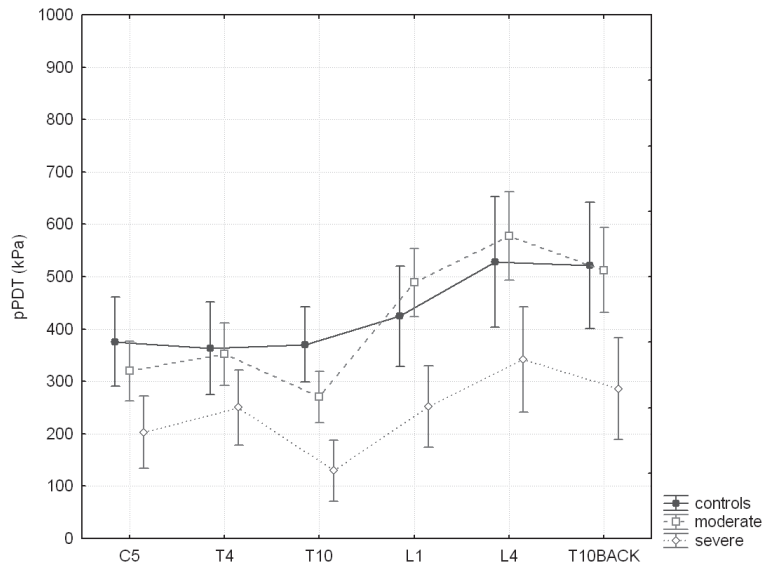
All values are means with standard deviations unless mentioned otherwise. Percentages may not total 100 due to rounding. †Weak analgesics were defined as NSAIDS, paracetamol, codeine and tramadol. Strong analgesics were defined as opioid-based therapies. 'MEQ' is morphine equivalents per day. Values marked with an asterisk were significantly different from each other.

Thresholds to pressure stimulation

For pPDT, there were significant differences between groups overall (GROUP; $F = 8.88$, $P < 0.001$). Post hoc analysis showed overall significantly lower thresholds for the severe chronic pancreatitis group compared to healthy controls ($P = 0.001$) and moderate pancreatitis group ($P < 0.001$). As expected, thresholds were significantly different according to dermatome of measurement (SITE; $F = 45.28$, $P < 0.0001$). A significant interaction was found for SITE and GROUP ($F = 3.75$, $P < 0.0001$) (Figure 2). Post hoc

analysis showed significantly lower thresholds for dermatome L1 (P = 0.04), L4 (P = 0.04) and T10BACK (P = 0.05) in the severe chronic pancreatitis group compared to the moderate chronic pancreatitis group.

Figure 2
Pressure pain detection thresholds

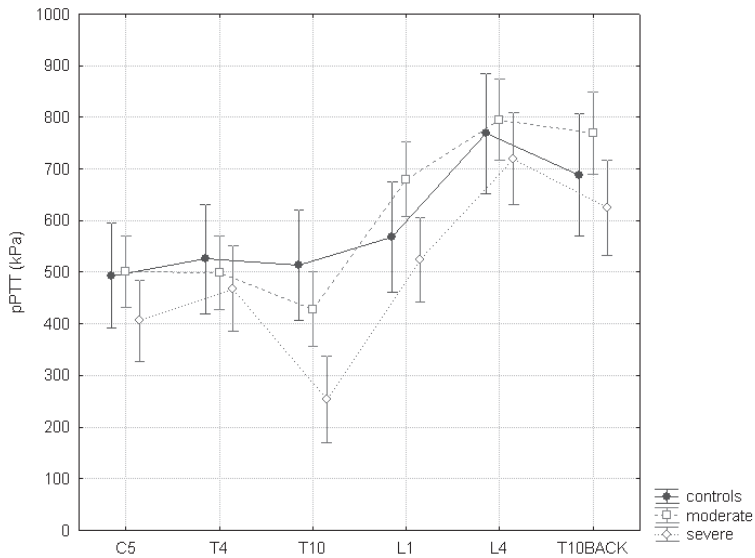


The horizontal axis shows all six dermatomes, the vertical axis shows pressure pain detection thresholds (pPDT) in kPa.
Results are means with 95% confidence intervals. 'Controls' is healthy control group, 'moderate' is moderate chronic pancreatitis group and 'severe' is severe chronic pancreatitis group. The difference between study groups and all six dermatomes for pPDT is significant (F = 3.75, P < 0.0001).

For pPTT there were no significant thresholds differences between groups overall, but only a trend (GROUP; F = 2.99, P = 0.06). Thresholds in the different dermatomes again significantly differed (SITE; F = 80.72, P < 0.0001). A significant interaction between SITE and GROUP (F = 3.27 and P < 0.001) was seen (Figure 3). However post hoc analysis was not significant, with only a trend to lower thresholds between the severe pancreatitis group and healthy controls for the pancreatic dermatome (P = 0.07).

FIGURE 3

Pressure pain tolerance thresholds



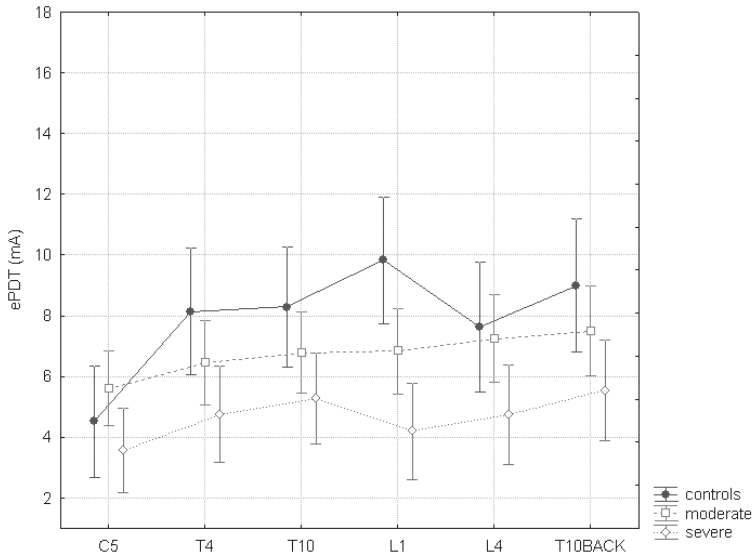
The horizontal axis shows all six dermatomes, the vertical axis shows pressure pain tolerance thresholds (pPTT) mentioned in kPa.
Results are means with 95% confidence intervals. Controls' is healthy control group, 'moderate' is moderate chronic pancreatitis group and 'severe' is severe chronic pancreatitis group. The difference between study groups and all six dermatomes for pPTT is significant ($F = 3.27$, $P < 0.001$).

Thresholds to electrical stimulation

ePDT thresholds differed significantly according to dermatome (SITE; $F = 17.48$, $P < 0.0001$) and groups overall (GROUP; $F = 4.34$, $P = 0.02$). Post hoc analysis for GROUP showed overall significantly lower thresholds for the severe chronic pancreatitis group compared to healthy controls ($P = 0.007$) and for the severe chronic pancreatitis group compared to the moderate chronic pancreatitis group ($P = 0.03$). There was also a significant interaction between SITE and GROUP ($F = 3.72$, $P < 0.0001$) (Figure 4). Post hoc analysis was not significant, with only a trend to lower thresholds for the severe pancreatitis patients in L1 compared to healthy controls ($P = 0.053$), but without obvious difference between other dermatomes.

FIGURE 4

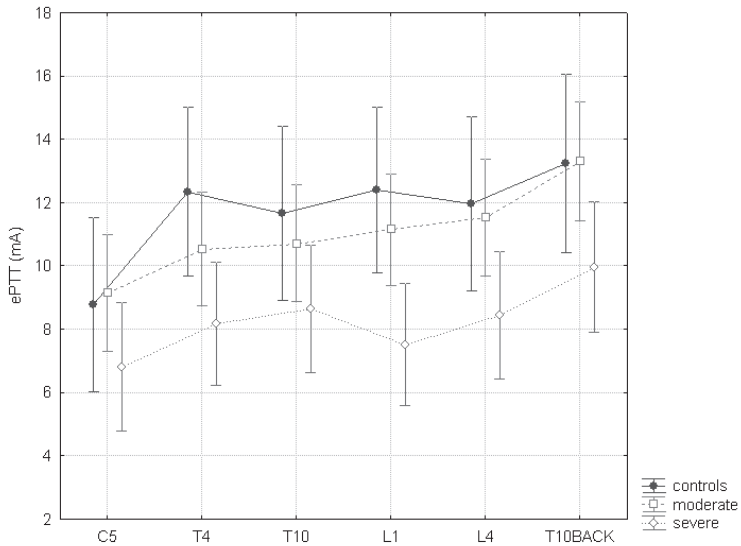
Electric pain detection thresholds



The horizontal axis shows all six dermatomes, the vertical axis shows electric pain detection thresholds (ePDT) in mA.
Results are means with 95% confidence intervals. 'Controls' is healthy control group, 'moderate' is moderate chronic pancreatitis group and 'severe' is severe chronic pancreatitis group. The difference between study groups and all six dermatomes for ePDT is significant ($F = 3.72$, $P < 0.0001$).

For ePTT thresholds differed significantly for GROUP ($F = 3.9$, $P = 0.03$), with again a significant post hoc analysis for overall lower thresholds for the severe chronic pancreatitis group compared to healthy controls ($P = 0.02$) and for the severe chronic pancreatitis group compared to the moderate chronic pancreatitis group ($P = 0.02$). Thresholds differed significantly for SITE ($F = 12.98$, $P < 0.0001$). The interaction between SITE and GROUP was not significant ($F = 0.91$, $P = 0.53$) (Figure 5).

FIGURE 5
Electric pain tolerance thresholds



The horizontal axis shows all six dermatomes, the vertical axis shows electric pain tolerance thresholds (ePTT) in mA.
Results are means with 95% confidence intervals. 'Controls' is healthy control group, 'moderate' is moderate chronic pancreatitis group and 'severe' is severe chronic pancreatitis group. The difference between study groups and all six dermatomes for ePTT is non-significant (F = 0.91, P = 0.53).

Conditioned pain modulation

The baseline pressure pain tolerance thresholds for dermatome L4 were not significantly different between groups (pPTT L4; F = 0.8, P = 0.45). Chronic pancreatitis patients and healthy controls showed an increase in thresholds after the cold pressor task. The moderate chronic pancreatitis patients tolerated the cold pressor task for 66 ± 59 sec and the severe chronic pancreatitis patients for 36 ± 27 sec versus healthy controls with 180 ± 1 sec – which was significantly different overall (F = 52.2, P < 0.0001). Post hoc analysis was only significant for the healthy controls versus the two pancreatitis groups (P < 0.0001).
The effect of CPM was smaller in the patient groups compared to the controls, but the difference between groups was not significant (GROUP; F = 2.2, P = 0.13; controls: mean 32.8% ± 8.9% vs. moderate: 13.5% ± 21.4% vs. severe: 10.3% ± 39.9%). When all pancreatitis patients were taken together and compared to healthy controls, there was a significant difference (P = 0.04; controls: mean 32.8% ± 8.9% vs. pancreatitis: 12.0% ± 4.8%).

DISCUSSION

Our study confirms that patients with chronic pancreatitis show signs of central sensitization, manifest as lower pain thresholds compared to healthy controls. Our results suggest that patients with more severe disease exhibit more central sensitization. We were unable to demonstrate a relation between disease stage and effectiveness of inhibitory pain modulation.

Altered pain processing

Peripheral nociception at the site of the pancreas spreads via ascending pathways of the spinal cord to supraspinal structures including the cortex.[27,28] If neurons at the spinal cord undergo neuroplastic changes, these changes will typically manifest as segmental hyperalgesia in the corresponding segments.[11,29] Increased nociceptive drive on secondary neurons leading to hyperexcitability and firing of supraspinal neurons at lower thresholds can then be expected to ultimately result in spreading and generalized hyperalgesia.[11] Our findings are compatible with the above described changes and EEG studies in chronic pancreatitis pain patients showing alterations in the organization of the pain matrix.[10,30] The main interest of our study is its provision of first evidence that patterns of altered pain processing may also reflect disease stage and progression.

The effect of endogenous feedback systems on nociceptive input can be measured using the CPM paradigm, which reflects effects of descending control from the brain on second-order neurons in the spinal cord.[31] Recent evidence suggests that patients with chronic painful diseases like chronic pancreatitis may exhibit less effective descending inhibitory control.[21,32] Our study confirms this result.

Both peripheral and central pain signaling are potentially sensitized in chronic pancreatitis. Several studies provide evidence for peripheral visceral nerve damage in chronic pancreatitis.[11] The presence of central sensitization demonstrated in chronic pancreatitis patients in the present study (and others) means that pain signaling is exaggerated in the central nervous system too. This central sensitization can be due to either a direct increase of sensitivity of neural structures, or due to a loss of inhibitory modulation of neural structures. The latter is tested by the CPM paradigm and was unaffected by disease stage but greater in chronic pancreatitis patients versus healthy controls. The lacking effect of disease stage on CPM could be real or due to lacking study power in the face of greater variability in CPM measures as compared to pain thresholds.[33] Clearly this topic needs further investigation in a larger patient collective.

Clinical implications

The findings concerning variations in supraspinal central sensitization in relation to disease stage suggest implications regarding treatment approaches in chronic pancreatitis. Firstly,

it has been demonstrated that degree of hyperalgesia in neuropathic pain patients is inversely related to analgesic efficacy of opioids.[34] If this applies in chronic pancreatitis, then increasing hyperalgesia will be linked to decreasing analgesic efficacy of opioids – and probably also increased risk of opioid-induced hyperalgesia.[35] Secondly, therapeutic measures aimed at nociceptive deafferentation alone (e.g. splanchnic denervation, surgery aimed at specific anatomical causes, peripheral analgesia) are unlikely to be effective unless combined with specific treatments targeting central sensitization (e.g. gabapentinoids, tricyclic antidepressants and ketamine).[2,7,11,36,37] This is again more likely to be the case in patients with more hyperalgesia, which in turn appears related to disease stage. Finally, there are indications that long-term, ongoing nociceptive input may result in supraspinal alterations to pain processing becoming independent of peripheral nociceptive input (autonomy).[6] This likely renders therapeutic measures aimed at depressing peripheral nociceptive input ineffective, making treatment of altered central pain processing the foundation of pain treatment in these patients.[2,11] Such a course of events leading to autonomy would appear more likely in patients with more hyperalgesia and a longer history of their disease – and may again be related to disease stage. The diagnostic and therapeutic implications of these observations deserve further study.

Other chronic pain disorders

Our results support the hypothesis that patients with more severe disease exhibit more central sensitization. This hypothesis is further supported by other studies regarding relationships between disease severity, degree of central sensitization and therapeutic effect. For complex regional pain syndrome, a clear relationship between degree of central sensitization and disease progression has been demonstrated.[38] In inflammatory bowel disease and endometriosis a relation has been found between segmental or generalized hyperalgesia as a sign of central sensitization and clinical difficulty in controlling pain.[16,22,39] Similar results have been described in the past in Crohn's disease and ulcerative colitis, where the degree of central sensitization was related to extent of bowel inflammation.[40-43] Clearly more research is needed in chronic pain patients to establish the relation between disease severity, changes in the central nervous system processing and therapeutic success. As a result of this, recently we started a longitudinal observational study with serial QSTs in chronic pancreatitis patients who are early in their disease to describe changes in pain processing during disease progression.

Methodological considerations

A limitation of this study is the relatively small size of the two chronic pancreatitis disease stage subgroups. Nevertheless, even the present explorative study provides evidence

of significant differences between healthy controls and a validated classification of pancreatitis disease stages. A better powered study might have provided more robust and significant evidence across all the modalities and individual dermatomes we measured in our study.

Sensitization of neurons and the extent of sensitization could be different between different tissues (skin vs. deeper tissues) and dermatomes. This might explain the differences between electric pain thresholds (a more superficial stimulus) and pressure pain thresholds (a stimulus of deeper tissues) in different dermatomes.

The healthy control group is slightly younger than the pancreatitis group. However, the impact of aging on pain processing remains controversial, some studies described an increase of pain thresholds during aging[44], others showed no effect[45] and some showed a decrease in thresholds during aging.[46]

A further important limitation of this study is that it is only cross-sectional. For definitive answers, a larger and longitudinal study will need to be performed. In this study only QST measurements were performed. Combining QST with EEG measurements or brain imaging would provide more detailed data on changes in the central nervous system in relation to pain processing on which to base more effective therapeutic strategies in the future. The M-ANNHEIM classification is at the moment the most comprehensive classification system for different stages of chronic pancreatitis and various degrees of clinical severity. In our study the classification proved simple, objective and accurate to apply.[26]

Conclusion and summary

The present study confirms that chronic pancreatitis patients show signs of altered central processing of nociception compared to healthy controls. The study further suggests that these changes may be influenced by disease stage. These findings underline the need to take altered central pain processing into account when managing the pain of chronic pancreatitis and may have important implications for its treatment. More research is needed to further characterize the link between disease severity and progression and its relationship to altered pain processing and treatment in chronic pancreatitis and other chronic pain disorders.

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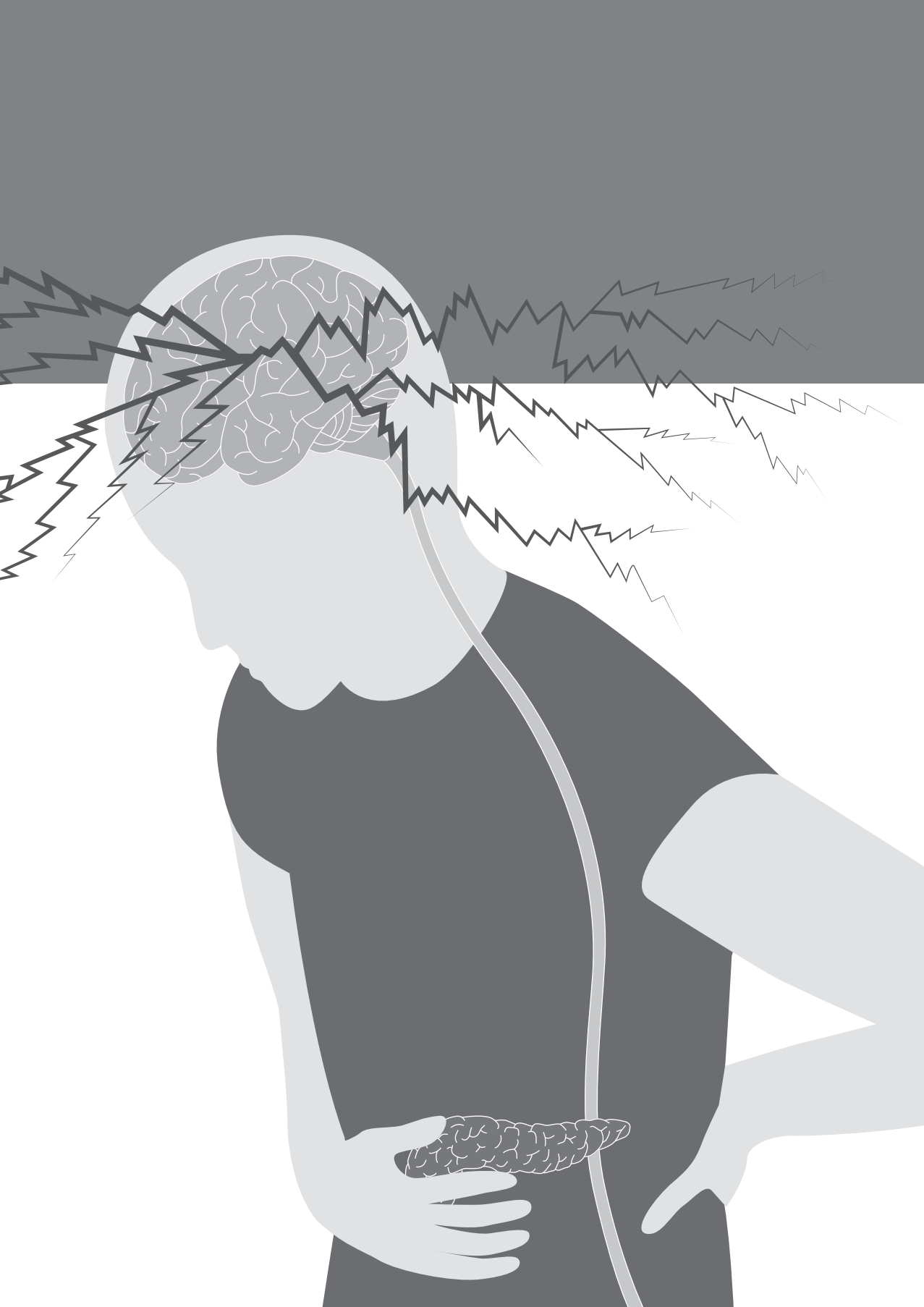

Chapter 4

Altered central pain processing after pancreatic surgery for chronic pancreatitis

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ABSTRACT

Background

Chronic abdominal pain is common in chronic pancreatitis and may involve altered central pain processing. This study evaluated the relationship between pain processing and pain outcome after pancreatic duct decompression and/or pancreatic resection in patients with chronic pancreatitis.

Methods

Patients with chronic pancreatitis underwent quantitative sensory testing. Pain processing was measured via electrical pain detection (ePDT) and electrical pain tolerance (ePTT) thresholds in dermatomes C5 and L4. Inhibitory descending pain control mechanisms were assessed using the conditioned pain modulation (CPM) paradigm. Healthy controls and patients with chronic pancreatitis were compared, and patients with chronic pancreatitis and a poor pain outcome (visual analogue scale (VAS) score greater than 30) were compared with those with a good pain outcome (VAS score 30 or less).

Results

Forty-eight patients with chronic pancreatitis had lower ePDT, ePTT and CPM responses compared with values in fifteen healthy controls ($P < 0.030$). The sum of ePDT values was lower in patients with a poor pain outcome than in those with a good outcome (median 7.1 chronic pancreatitis vs. 11.2 mA; $P = 0.008$). There was a correlation with the VAS score and the sum of ePDT values ($rs = –0.45$, $P = 0.016$) and ePTT values ($rs = –0.46$, $P = 0.011$), and CPM response ($rs = –0.43$, $P = 0.006$) in patients with chronic pancreatitis.

Conclusion

After pain-relieving pancreatic surgery, patients with chronic pancreatitis exhibit altered central pain processing compared with that in healthy controls. Poor pain outcomes are associated with more central sensitization and more pronociceptive descending pain modulation, and this should be considered when managing persistent pain after pain-relieving surgery for chronic pancreatitis.

INTRODUCTION

Pain control in chronic pancreatitis can be a challenge.[1,2] As pain progresses during the course of chronic pancreatitis, a substantial group of patients have multiple endoscopic and/or surgical interventions in an attempt to alleviate the pain.[3-7] Even when these invasive procedures are technically successful, some patients continue to suffer pain. This group of patients tends to be refractory to further classical pain management, exhibiting opioid dependence, failure of nerve blockade, recurrent hospitalization and impaired quality of life.[1,8,9]

A possible explanation for this type of intense chronic pain involves changes in the central nervous system due to chronic nociceptive input.[10] Ongoing nociceptive input, caused by nerve damage and local inflammation, is increasingly recognized to result in altered pain processing at spinal and supraspinal levels of the central nervous system.[11,12] Together with the loss of descending inhibitory control mechanisms and activation of descending facilitation, this central sensitization is manifest as generalized hyperalgesia.[13] Ultimately, these changes may become independent of nociceptive input, thus maintaining the chronic pain state.[14]

Accumulating evidence supports this view of chronic pain in chronic pancreatitis.[9,10,15,16] Insight into various aspects of pain processing in patients with chronic pancreatitis has been gained using experimental pain models and explored by quantitative sensory testing (QST), electroencephalography or (functional) magnetic resonance imaging ((f) MRI).[9,10,17-19] These approaches are further supported by recent findings demonstrating that treatment with S-ketamine infusion, pregabalin and thoracoscopic splanchnicectomy is accompanied by a reduction in generalized hyperalgesia.[15,16,18]

Based on the hypothesis that poor clinical pain outcomes after pancreatic surgery are associated with more central sensitization and less effective inhibitory modulation, the aim of this study was to explore the relationship between pain outcomes based on pain experience and altered central pain processing in patients with chronic pancreatitis who had undergone pancreatic surgery for pain relief, in the hope of being able to target and design more effective therapies for this group.

METHODS

Consecutive patients with chronic pancreatitis who underwent pancreatic surgery for pain were identified from electronic registries for surgical procedures at three Dutch university hospitals with special interest in the treatment of chronic pancreatitis (Radboud university nijmegen medical center, University Medical Centre Utrecht and Erasmus MC). The period of inclusion varied from eight to fifteen years between centers. Inclusion criteria were confirmed diagnosis of chronic pancreatitis and that the primary indication

for surgery was pain. All patients were aged eighteen years or more.
Patients included in the study underwent either a drainage procedure (pancreatico-jejunostomy), a duodenum-preserving pancreatic head resection (Beger or Frey procedure), a pancreaticoduodenectomy or a left-sided pancreatic resection (tail resection).[20-22] The indication for the type of surgery was based on the location of pathological changes in the pancreas on preoperative computed tomography or MRI. All procedures were considered a technical success by the operating surgeon. Patients with other indications for pancreatic surgery, previous pancreatic surgery and known malignancy at time of operation were excluded. None of the patients had a new endoscopic or surgical intervention after the pancreatic drainage or resection procedure.
For inclusion in the study, patients needed to have a history of chronic abdominal pain typical of pancreatitis (dull epigastric pain more than three days per week for at least three months) and a diagnosis of chronic pancreatitis based on the Mayo Clinic diagnostic criteria.[5]
The local institutional review board waived the need for formal ethics committee approval because the study was purely observational, and because the QST measurements were performed routinely in patients with chronic pain in these institutions. Subjects gave informed consent to participate. The study was conducted according to the guidelines of the Central Committee on Research involving Human Subjects in the Netherlands and the principles outlined in the Declaration of Helsinki.[23]
A healthy control group recruited for an earlier trial was used to confirm the presence of spreading hyperalgesia in the chronic pancreatitis group.[18] Control subjects had no history of a medical condition that could alter pain processing or interfere with pain measurements.

Clinical data

Pain was assessed using a 0 – 100 visual analogue scale (VAS), with a score of zero being no pain and 100 the worst imaginable pain.[24] Patients with chronic pancreatitis were allocated to either a poor (score above 30) or good (score 30 or less) pain outcome group based on their postoperative VAS score. The Izbicki pain score was measured during outpatient visits.[25] Baseline characteristics consisted of age, sex, duration of pain symptoms before surgery, preoperative and postoperative use of opioid analgesics, type of surgical procedure, time from operation until measurement and continued alcohol or tobacco use.[26-28]

Quantitative sensory testing

QST was performed by technicians who were blinded for group allocation, using a standard temporal test sequence.[10] Testing in women was not standardized with regard to phase

of the menstrual cycle because all of the female patients were amenorrhoeic. All patients were asked to fast before testing. After initial QST training, electrical pain detection (ePDT) and electrical pain tolerance (ePTT) thresholds to constant-current electrical skin stimulation (Digistim; Biometer, Copenhagen, Denmark), tetanic stimulation at 100 Hz, 0.2 ms square waves, self-adhesive electrodes 3 cm apart, were obtained at each of the following sites on the dominant body side: lower neck (C5 dermatome) and knee (L4 dermatome), on the basis that both dermatomes are distant from the pancreatic dermatome and were chosen to observe spreading (or generalized) hyperalgesia.[15]
The conditioned pain modulation (CPM; previously known as diffuse noxious inhibitory control (DNIC)) paradigm was performed to test the ability of the patient to generate descending inhibitory modulation.[29,30] The ePTT (test stimulus) was determined before and after the cold pressor task (conditioning stimulus), and the CPM effect was determined as the relative (percentage) change in ePTT. A negative CPM response implies pronociceptive descending pain modulation. For the cold pressor task, the dominant hand was immersed in ice-chilled water (1.0 °C ± 0.3 °C). The patient was told to remove their hand from the water after two min of immersion, or sooner if the pain was considered to be intolerable, and the immersion time was noted. Immediately after the cold pressor task, subjects rated the pain experienced during the test by use of a VAS for quality control purposes. The ePTT in the non-dominant L4 dermatome (knee) was obtained immediately before and after ice water immersion.

Outcome measures

The primary effect parameter for the study was the difference in the sum of electrical pain threshold values for all dermatomes between the two pain outcome groups and the healthy controls.[15] Secondary endpoints were the differences in pain thresholds for the individual dermatomes and in CPM response between the pain outcome groups and healthy controls.

Statistical analysis

Statistical analysis was performed using the software package STATISTICA for Windows, release 7.0 (StatSoft, Tulsa, Oklahoma, USA). Non-normally distributed data are presented as median with interquartile ranges (IQR). The sum of electrical pain detection and tolerance thresholds for all dermatomes, and the CPM results were compared between healthy controls and all patients with chronic pancreatitis using the Mann–Whitney U test, to confirm spreading hyperalgesia in patients with chronic pancreatitis.
For the chronic pancreatitis group as a whole, correlations between VAS pain score and the sum of thresholds and individual dermatomal thresholds were determined by Spearman's rank correlation coefficient. Statistical significance was set at $P \leq 0.050$.

Subsequent comparisons between good and poor pain outcome groups, and healthy controls for (sum of) thresholds, change in (sum of) thresholds and CPM were conducted with the Mann–Whitney U test with the Bonferroni correction for multiple comparisons (good vs. poor outcome, healthy controls vs. good outcome, and healthy controls vs. poor outcome). Statistical significance was set at $P \leq 0.020$.

The Mann–Whitney U test was used to analyze differences in QST pain thresholds between opioid and non-opioid users. The Kruskal–Wallis test was used for analysis of differences in QST pain thresholds for opioid and non-opioid users within the good and poor pain outcome groups (four groups). A similar analysis was performed for three other subgroups: cigarette smokers and non-smokers, alcohol and non-alcohol users, and patients with and without glucose levels above 10 mmol/l (180 mg/dl).

RESULTS

Enrollment and baseline characteristics

From September 2008 to March 2011, a total of 76 patients with chronic pancreatitis were screened and 48 recruited from a Dutch study describing clinical outcome in relation to timing of surgery in chronic pancreatitis.[31] Patients declined to participate for a variety of reasons: travelling distance, no personal benefit and active relapse of chronic pancreatitis. All recruited patients (13 women and 35 men of median age 49 (IQR 42 – 57)) years completed the measurements according to the protocol and were analyzed. The median pain VAS score at time of examination was 43 (IQR 12 – 68) and the median Izbicki pain score was 56 (IQR 25 – 70). Twenty-three patients (48%) used opioids, with a median opioid consumption of 45 (IQR 11 – 90) mg morphine equivalents per day. The median time from operation to QST measurement was 66 (IQR 44 – 115) months. Thirty-seven patients (77%) had a glucose level below 10 mmol/l immediately before testing. The healthy control group consisted of fifteen volunteers (7 women and 8 men of median age 38 (IQR 35 – 49) years). Healthy controls were younger than chronic pancreatitis patients ($P < 0.001$).

Patients with chronic pancreatitis versus healthy controls

Electrical pain thresholds

The sum of threshold values for electrical pain detection and tolerance was significantly lower in the chronic pancreatitis group than in healthy controls ($P = 0.024$ and $P = 0.001$ respectively).

Individual ePDT values in dermatome L4 and ePTT values in dermatome L4 were all significantly lower for patients with chronic pancreatitis than for healthy controls ($P = 0.007$ and $P < 0.001$ respectively). Individual ePDT values in dermatome C5 were

significantly lower in the chronic pancreatitis group than in the control group (P = 0.030). Only individual ePTT values for dermatome C5 were not significantly lower between the groups (P = 0.177).

Taken together, these results indicate that, compared with healthy controls, patients with chronic pancreatitis exhibit generalized hyperalgesia to electrical stimulation (Table 1).

TABLE 1

Baseline quantitative sensory testing values in all patients with chronic pancreatitis versus healthy controls

	Chronic pancreatitis	Healthy controls	P-value*
ePDT (mA)			
Sum of dermatomes	8.2 (5.1 – 11.4)	11.2 (8.8 – 17.7)	0.024
Dermatome C5	3.7 (2.9 – 5.6)	4.9 (3.4 – 7.2)	0.030
Dermatome L4	4.6 (2.8 – 5.9)	6.3 (4.7 – 11.1)	0.007
ePTT (mA)			
Sum of dermatomes	11.7 (9.4 – 15.3)	21.6 (13.7 – 27.9)	0.001
Dermatome C5	5.6 (4.6 – 8.0)	8.2 (5.6 – 12.1)	0.177
Dermatome L4	6.1 (4.3 – 7.2)	12.1 (8.1 – 15.9)	< 0.001
CPM			
Latency (sec)	72 (26 – 180)	180 (180 – 180)	< 0.001
Response (%)	–2.7 (–22.1 – 30.1)	32.6 (10.4 – 41.8)	0.004

Values are medians with interquartile ranges. 'ePDT' is electrical pain detection threshold, 'ePTT' is electrical pain tolerance threshold and 'CPM' is conditioned pain modulation. *Mann–Whitney U test.

Conditioned pain modulation response

At baseline, patients with chronic pancreatitis tolerated the cold pressor task for shorter periods than healthy controls (P < 0.001). Subjects in the healthy control group exhibited a significantly greater CPM response than patients with chronic pancreatitis (P = 0.004) (Table 1). These results indicate that patients with chronic pancreatitis have less effective descending inhibitory modulation than healthy controls.

Correlations

For the chronic pancreatitis group as a whole, a significant negative correlation was found between the VAS score and the sum of ePDT values (rs = –0.45, P = 0.016) and the sum of ePTT values (rs = –0.46, P = 0.011).

There were also significant negative correlations with ePDTs for L4 (rs = –0.48, P = 0.009) and ePTTs for C5 (rs = –0.50, P = 0.004), and a negative correlation between the VAS score and CPM response (rs = –0.43, P = 0.006).

TABLE 2

Characteristics of patients with chronic pancreatitis with good versus poor pain outcome

	Good pain outcome (N = 18)	Poor pain outcome (N = 30)
Age (years)*	53 (41 – 58)	48 (42 – 54)
Sex ratio, male:female - no.	14 : 4	21 : 9
Etiology		
Alcohol	9 (50)	18 (60)
Biliary	3 (17)	6 (20)
Other	6 (34)	6 (20)
Surgery		
Pancreaticojejunostomy	1 (6)	3 (10)
Tail resection	4 (22)	6 (20)
Frey procedure	6 (33)	4 (13)
Beger procedure	6 (33)	10 (33)
Pancreaticoduodenectomy	1 (6)	7 (23)
Body mass index (kg/m^2)*		
Preop.	20.6 (18.9 – 22.8)	21.3 (18.8 – 23.3)
Postop.	22.8 (20.8 – 24.1)	22.5 (19.5 – 26.8)
Preop. duration of symptoms (days)*	27 (11 – 78)	50 (17 – 100)
Relapse after operation (weeks)		
> 15	1 (6)	1 (3)
8 - 15	1 (6)	2 (7)
< 8	0 (0)	0 (0)
Postop. alcohol use	9 (50)	10 (33)
Postop. smoking	14 (78)	17 (57)
Opioid use		
Preop.	9 (50)	22 (73)
Postop.	7 (39)	16 (53)
Postop. endocrine insufficiency	9 (50)	22 (73)†
Postop. exocrine insufficiency	13 (72)	23 (77)
New-onset diabetes mellitus	6 (33)	15 (50)
Postop. VAS score*	8 (0 – 16)	65 (49 – 74)‡
Postop. Izbicki pain score*	23 (0 – 54)	64 (53 – 77)‡
Postop. time to QST* (weeks)	88 (55 – 109)	59 (40 – 121)

Values in parentheses are percentages unless indicated otherwise; *values are medians with interquartile ranges. 'VAS' is visual analogue scale and 'QST' is quantitative sensory testing. †P = 0.038, ‡P < 0.001 (Mann–Whitney U test).

Good versus poor pain outcome group

Eighteen patients with chronic pancreatitis and a postoperative VAS score of 30 or less were allocated to the good pain outcome group. The other 30 patients had a VAS score above 30 and were allocated to the poor pain outcome group. The two groups were comparable for baseline characteristics, except for the incidence of postoperative endocrine insufficiency, which was significantly higher in patients with a poor pain outcome. VAS and Izbicki pain scores were also significantly higher in the poor pain outcome compared with the good pain outcome group (Table 2).

Electrical pain thresholds

The sum of ePDT values for all dermatomes was significantly lower in the poor pain outcome group than in the good pain outcome group (P = 0.008). The sum of ePTT values was also lower in patients with poor pain outcomes, although the difference was not significant (P = 0.051).

For individual dermatomes, electrical pain detection and tolerance thresholds were significantly lower (ePDT L4, P = 0.003), or lower without reaching significance (ePDT C5, P = 0.039; ePTT C5, P = 0.028; ePTT L4, P = 0.079), for poor pain outcome versus good pain outcome (Table 3).

Based on these results, patients with poor pain outcome are hyperalgesic compared with those with a good pain outcome for some measurements.

Conditioned pain modulation response

Clear differences were seen in the cold pressor task latency and CPM response, but these results did not reach statistical significance (Table 3).

Good pain outcome group versus healthy controls

Electrical pain thresholds

No difference in the sum of ePDT values was observed between patients with a good pain outcome and healthy controls. The sum of ePTT values was significantly lower in the good pain outcome group (P = 0.019), but individual dermatomal ePTTs were significantly lower only for dermatome L4 (P = 0.003).

Conditioned pain modulation response

Patients with a good pain outcome tolerated the cold pressor task for a much shorter time than healthy controls (P = 0.001), although the CPM response was comparable between these two groups (Table 3).

TABLE 3

Comparison of baseline quantitative sensory testing results in patients with chronic pancreatitis with good and poor pain outcome, and in healthy controls

	Good pain outcome	Poor pain outcome	P-value*	Healthy controls	P-value†	P-value‡
ePDT (mA)						
Sum of dermatomes	11.2 (10.0 – 12.3)	7.1 (4.7 – 9.5)	0.008	11.2 (8.8 – 17.7)	0.726	0.004
Dermatome C5	5.2 (3.9 – 6.4)	3.4 (2.6 – 4.7)	0.039	4.9 (3.4 – 7.2)	0.953	0.06
Dermatome L4	5.9 (4.7 – 7.3)	3.2 (2.3 – 5.1)	0.003	6.3 (4.7 – 11.1)	0.482	0.001
ePTT (mA)						
Sum of dermatomes	13.1 (11.5 – 18.0)	11.3 (6.9 – 14.5)	0.051	21.6 (13.7 – 27.9)	0.019	0.001
Dermatome C5	6.9 (5.3 – 8.6)	4.8 (4.2 – 7.4)	0.028	8.2 (5.6 – 12.1)	0.274	0.014
Dermatome L4	6.5 (5.7 – 8.0)	4.6 (3.4 – 6.6)	0.079	12.1 (8.1 – 15.9)	0.003	< 0.001
CPM						
Latency (s)	113 (42 – 180)	40 (25 – 180)	0.316	180 (180 – 180)	0.001	< 0.001
Response (%)	21.3 (–5.8 – 37.1)	–12.1 (–40.1 – 21.1)	0.021	32.6 (10.4 – 41.8)	0.167	0.001

Values are medians with interquartile ranges. 'ePDT' is electrical pain detection threshold; 'ePTT' is electrical pain tolerance threshold; 'CPM' is conditioned pain modulation. *Good versus poor pain outcome; †healthy controls versus good pain outcome; ‡healthy controls versus poor pain outcome (Mann–Whitney U test with Bonferroni correction for multiple comparisons; $P \leq 0.02$ was considered statistically significant).

Poor pain outcome group versus healthy controls

Electrical pain thresholds

The sum of ePDT and the sum of ePTT values were significantly decreased in patients with a poor pain outcome compared with healthy controls (P = 0.004 and P = 0.001 respectively).

ePDTs in dermatome L4 and ePTTs in dermatomes C5 and L4 were all significantly lower in the poor pain outcome group compared with values in healthy controls (P = 0.001, P = 0.014 and P < 0.001 respectively).

Conditioned pain modulation response

The length of time for which patients with a poor pain outcome tolerated the cold pressor task was much shorter than that for healthy controls (P < 0.001). CPM response was decreased in patients with a poor pain outcome (P = 0.001) (Table 3).

Subgroup analysis

No significant differences for electrical pain thresholds (individual and sum of threshold values) or CPM response were observed for the subgroups of opioid and non-opioid users within the good and poor pain outcome groups. Neither were there any significant differences between cigarette smokers and non-smokers, alcohol and non-alcohol users, and patients with and without glucose levels above 10 mmol/l for electrical pain thresholds and CPM response. Testing for these three variables within the good and poor pain outcome groups revealed no differences in QST pain thresholds.

DISCUSSION

Patients with chronic pancreatitis who had a good pain outcome (low VAS score) after pancreatic surgery still exhibited some signs of hyperalgesia compared with healthy controls. Those with poor pain outcome scores after surgery, however, showed generalized hyperalgesia and a reduced CPM response compared with healthy controls. When patient groups with a good or poor pain outcome were compared, the poor outcome group also showed lower pain thresholds, suggesting generalized hyperalgesia. Together with the negative correlations between VAS score and pain thresholds/CPM response, these data suggest that the degree of pain reported by patients with chronic pancreatitis after pancreatic surgery may correlate with the severity of pronociceptive changes in central pain processing.

Sensitization of the nervous system is a cardinal feature of most chronic pain disorders.[13] Nociception from the pancreas spreads via local nerves and the spinal cord to supraspinal structures including the cortex. Changes in peripheral nerves and the central nervous

system may cause an increase in nociception and failure of protective mechanisms to inhibit nociception, resulting in more intense pain and widespread hyperalgesia.[9] Neuroplastic changes in local nerves and the dorsal horn of the spinal cord result in increased neuronal excitability, synaptic strength and neuronal reorganization.[9] Subsequently, changes in supraspinal processing lead to hyperexcitability and firing of supraspinal neurons at lower thresholds, manifest as spreading and ultimately generalized hyperalgesia.[9] Failure of systems that depress nociceptive activity (CPM) has been described for chronic pancreatitis.[32,33] Such failure is linked to persistent pain, which is often difficult to manage. All of these changes, taken together, carry the potential of independence from peripheral nociceptive input, where pain and hyperalgesia are no longer driven by peripheral nociceptive input.[11]

Patients with chronic pancreatitis who have a poor pain outcome after pancreatic surgery for pain relief show more aggressive pronociceptive alterations in pain processing, compared not only with healthy volunteers but also with patients who have a good pain outcome. This may be interpreted as a sign of (relative) independence of central sensitization from peripheral nociceptive input.[16] In these patients it might be that the source of nociceptive input (the pancreas) has been treated, but that changes in central pain processing persist, leading to ongoing pain. This subgroup of patients with poor pain outcomes is not uncommon in clinical practice, and is well described.[34-36]

Based on the theory described above, these patients should respond best to therapeutic measures targeting alterations in central nervous system processing, such as pregabalin for central sensitization or duloxetine to improve descending inhibitory modulation.[18,37] The present data also suggest that revisional surgery in patients with chronic pancreatitis with poor pain control is likely to have only limited effects on their pain. Increasing opioid doses in these patients often fails and may further enhance hyperalgesia.[1,8,9] Although in the present series there was no difference in opioid use between the good and poor pain outcome groups, neither was there a relationship within those groups between opioid usage and pain detection or tolerance thresholds. This may simply reflect the small numbers in these subgroup analyses.

There were reduced differences in pain thresholds for dermatome C5 between chronic pancreatitis and healthy control groups in comparison with the thresholds in dermatome L4 and the sum of thresholds. A possible explanation could be the mix of patients with good and poor pain outcomes in a single pancreatitis group. Patients with few pain symptoms showed far fewer QST abnormalities in the C5 dermatome than those with severe pancreatic pain, thereby increasing the QST values for the whole group. Once again, this may simply reflect small numbers in these small subgroups.

Comparison of these results with those for other chronic pain disorders could be relevant, but caution needs to be exercised owing to differences in etiology, disease

progression, symptoms and therapy. A few studies have documented postoperative pain after abdominal surgery and accompanying changes in central nervous system processing; these show that persistent postoperative pain is linked to a more sensitized central nervous system.[38-40] One study found that poorer preoperative inhibitory pain modulation was related to greater postoperative hyperalgesia and chronic pain.[41] Persistent pain after breast cancer surgery has been associated with alterations in central nervous system pain-modulatory processes[39], and hypersensitivity on the operated side was more prominent in patients with chronic postoperative pain after total hip arthroplasty.[40] Future work needs to identify prognostic factors related to changes in central nervous system processing that might then lead to effective strategies preventing pain persistence after surgery.

Limitations of this study are the retrospective data collection of patient characteristics and the single QST measurement after surgery. Prospective data collection and QST measurements before and after surgery would provide more complete insight into underlying mechanisms and processes. Owing to the absence of a control measurement before surgery, the impact of abdominal surgery alone on pain processing is difficult to assess and might be a confounding variable. Inability to determine the presence, absence or degree of hyperalgesia before intervention is a further weakness, as this is a feature that can affect chronic pain treatment outcomes.[10,15,16] A prospective longitudinal observational study of chronic pancreatitis during disease progression with serial QST measurements would provide more insight into pain processing and how this is influenced by different therapies.[16,41,42]

It is unlikely that the presence of acute on chronic pancreatitis or local complications after surgery influenced pain scores, as all patients came from home and were tested in an ambulatory outpatient setting. No patient had received or was scheduled for further treatments for any specific pancreatic or late surgical complications based on recent imaging.

Technical failure of the surgical procedures might be a confounding factor. This is unlikely because patients were specifically recruited where surgeons considered the operation to have been a technical success. Despite this, only 18 of the 48 patients had good pain outcome after pancreatic surgery. This is likely to involve some selection bias, as only a small proportion of patients with chronic pancreatitis were eligible for the study and those with a poor outcome may have been more willing to participate in a pain processing study. Another confounding factor could have been a difference in treatments between hospitals, but within the limitations of small numbers there was no evidence for this.

The marked pronociceptive central pain processing state seen in patients with a poor outcome suggests that a subgroup of patients has been identified in whom changes in central pain processing have become relatively independent of peripheral nociceptive

input. The clinical consequence of this finding is that patients with chronic pancreatitis with poor pain outcomes after surgery should undergo QST, and targeted drug treatment should be instituted if altered central pain processing is confirmed. This might involve ketamine and gabapentinoids for central sensitization, and tricyclic antidepressants for inadequate descending inhibitory modulation.[9,15,18,43] There is early evidence[15,18] to support such an approach, which seems logical based on monitoring of central processing via serial QST measurement, as this is generally accepted as an appropriate method to measure pain processing, is well standardized and validated for chronic pancreatitis.[10]
Identifying patients with autonomous pain processing is essential to improve the management of pain in chronic pancreatitis. These patients are more likely to benefit from treatments that target altered central pain processing rather than surgery.

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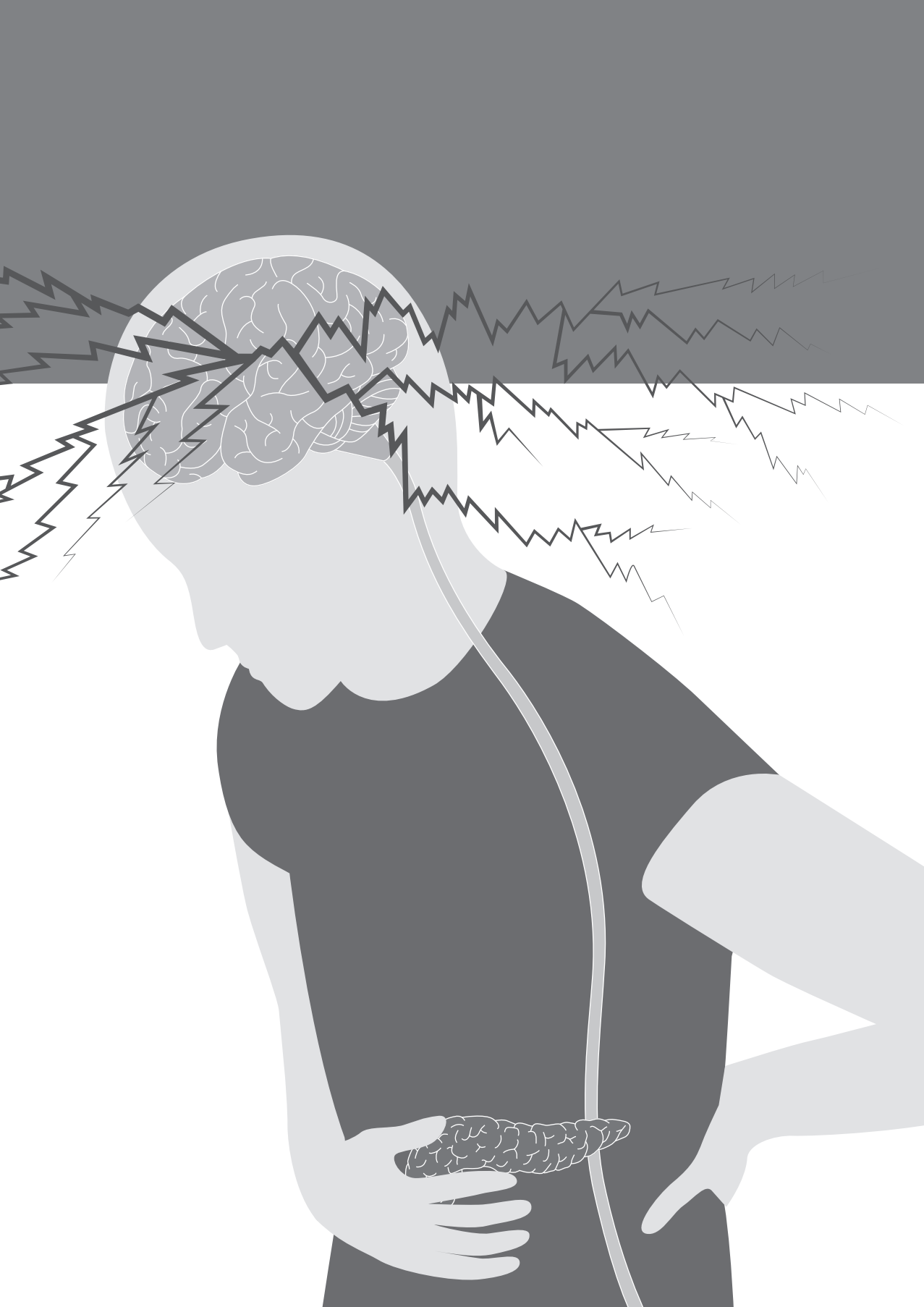

Chapter 5

Has central sensitization become independent of nociceptive input in chronic pancreatitis patients who fail thoracoscopic splanchnicectomy?

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ABSTRACT

Background and Objectives

Central sensitization due to visceral pancreatic nociceptive input may be important in chronic pancreatitis pain. We investigated whether bilateral thoracoscopic splanchnicectomy to reduce nociceptive input in chronic pancreatitis patients with poor pain control affects supraspinal and spinal sensitization.

Methods

Seventeen chronic pancreatitis patients were studied preoperatively and six weeks after bilateral thoracoscopic splanchnicectomy. Pressure pain thresholds (PPT) were measured in clavicle (C5) and pancreatic dermatomes reflecting supraspinal and spinal central sensitization, respectively. Patients with increased PPT after bilateral thoracoscopic splanchnicectomy (hypoalgesic) were compared to those without (hyperalgesic) and PPT versus pain numeric rating scale (NRS) changes compared.

Results

After bilateral thoracoscopic splanchnicectomy, ten patients showed C5 PPT increases (hypoalgesic; median change 87 kPa), seven patients had unaltered/lower PPT (hyperalgesic; -135 kPa). Preoperative pain NRS was similar between groups (4 vs. 5, $P = 0.2$). After bilateral thoracoscopic splanchnicectomy hypoalgesic group NRS was lower (1 vs. 6, $P = 0.008$) and NRS change greater (-2 vs. 0, $P = 0.005$). Whole group NRS and C5 PPT change correlated significantly and negatively ($rs = 0.53$, $P < 0.05$), but not for pancreatic PPT.

Conclusions

Reduced supraspinal – but not spinal – central sensitization after bilateral thoracoscopic splanchnicectomy was associated with significantly reduced pain scores in a majority of chronic pancreatitis patients. A subgroup showed no reductions in supraspinal central sensitization after bilateral thoracoscopic splanchnicectomy, coupled to no significant pain NRS reduction. Our results suggest that a subgroup of chronic pancreatitis patients with chronic pain has altered pain processing that may be independent of ongoing peripheral nociceptive input, resulting in persisting pain despite bilateral thoracoscopic splanchnicectomy. If confirmed, these results indicate the importance of sensory testing for indications and management of interventional pain treatments.

INTRODUCTION

Chronic pancreatitis is a disease characterized by progressive inflammation and irreversible fibrosis leading to destruction of pancreatic tissue.[1] Pain is the leading symptom in patients with chronic pancreatitis and the main reason for seeking medical help. Pancreatic surgery is often considered for pain relief when an anatomical substrate such as pancreatic duct dilation, pseudocyst and inflammatory mass are present.[2] Independently of the surgical treatment chosen, pain persists or relapses in 30% of the patients, leading to the need for ongoing analgesia and frequently to opioid dependence.[2,3] In these patients, pancreatic deafferentation, interrupting nociceptive input may be considered.[4] Such a minimally invasive procedure is bilateral thoracoscopic splanchnicectomy, which has high initial success rates and low morbidity rates.[5]

Ongoing nociceptive input, such as local inflammation or nerve damage, is now accepted to be one of the mechanisms that results in alterations of central sensory processing.[6] Loss of descending inhibitory control mechanisms or activation of descending facilitation favors nociceptive input and will lead to central sensitization, initially spinal and later on supraspinal.[7,8] Ultimately, central sensitization may become independent of peripheral nociceptive input, thus providing a plausible mechanism for the maintenance of chronic pain states in visceral pain patients.[7] Another mechanism could be opioid-induced hyperalgesia especially in patients on long-term opioid treatment.[9]

Using quantitative sensory testing (QST), we demonstrated that patients with chronic pancreatitis requiring long-term opioid therapy did have more central sensitization and generalized hyperalgesia than healthy controls.[10] These results suggest that central sensitization, due to visceral pancreatic nociceptive input, plays an important role in the pain of chronic pancreatitis, and that this process is often not effectively impacted by chronic opioid therapy.[10] There is evidence that bilateral thoracoscopic splanchnicectomy to reduce pancreatic nociceptive input may be effective in reducing central sensitization in such patients.[11] However, the fact that such deafferentation is not effective in all patients could imply that in some patients, such neuroplastic changes are independent of peripheral nociceptive input.[12,13]

The aim of the present study was to investigate, using QST, whether such independence of neuroplastic central alterations from ongoing peripheral nociceptive input exists. Our hypothesis is that pain in some chronic pancreatitis patients is related to alterations in pain processing, explaining the failure of splanchnicectomy in some chronic pancreatitis pain patients.

PATIENTS AND METHODS

Patients

At our unit we prospectively collect clinical and QST data from all chronic pancreatitis patients admitted. The present study is part of a clinical cohort of chronic pancreatitis patients scheduled for bilateral thoracoscopic splanchnicectomy and collected over the course of ten years. All these patients had severe continuous pancreatic pain (average daytime numeric rating scores (NRSs) ≥ 5) necessitating continuous opioid medication for the last six months. During this time, all had undergone several unsuccessful attempts to discontinue – or at least reduce – their opioid medication. Only patients on stable opioid therapy were selected to permit meaningful before-versus-after-surgery comparison.

In our hospital the performance of QST is part of routine clinical diagnostics and monitoring for the management of complex pain patients, for example chronic pancreatitis. Thus QST cannot be considered an intervention in the sense of an action that imposes extra risk or burden to the patient for study purposes. Hence no extra approval was necessary by our Ethics Committee (CMO region Arnhem-Nijmegen) because the study did not involve the collection of any extra data which was beyond standard clinical practice for our unit. Patients did provide informed consent for use of their clinical and QST data for study and publication purposes.

Patients with complications of chronic pancreatitis (e.g. biliary obstruction, pseudocysts) and patients with other acute or chronic pain syndromes (e.g. irritable bowel syndrome, migraine, complex regional pain syndrome I, fibromyalgia) were excluded. In cases of doubt an expert in chronic pain was consulted.

The patients' medical and demographic data were obtained from the patient records. Opioid medication for each patient was converted to morphine equivalents per day using the Narcotic Analgesic Converter (Version 2.0, GlobalRPh Inc.; www.GlobalRPh.com). We documented evidence of endocrine or exocrine pancreatic insufficiency together with chronic pancreatitis etiology (i.e. alcohol or non-alcohol).

Bilateral thoracoscopic splanchnicectomy

We used a technique adapted from that described by Cuschieri et al.[14] In summary, the procedure is performed under general anesthesia with double-lumen intubation for single lung ventilation. The patient is placed in the full prone jackknife position. The operating thoracoscope is introduced in the second intercostal space beneath the angle of the scapula. A second trocar is introduced one intercostal space above and a few inches towards the spine, and the pleural space opened from the 5th to the 12th thoracic vertebra. To ensure complete denervation, the splanchnic nerves and all the potentially nerve-bearing tissue on each side as well as the sympathetic chain are carefully transected using the harmonic scalpel (Ultracision, Johnson & Johnson

Medicals, Amersfoort, and the Netherlands). At the end of the procedure the lungs are re-expanded, and the trocar sites closed, without routine chest drains. Technical success was defined as 1) definitive visual identification of the splanchnic nerve branches between C5 and T12, the sympathetic chain, and the relevant nerve-bearing tissue; and 2) complete transection under visual control of these tissues.
All patients were treated according to a standard protocol for this intervention. So preoperative, perioperative and postoperative care was the same for every patient, as well for anesthetics used.

Clinical pain assessment and quantitative sensory testing
Measurements were performed one day preoperatively and six weeks after bilateral thoracoscopic splanchnicectomy. The clinical pain state was documented via verbal NRSs (0 = no pain and 10 = unbearable pain) obtained at the beginning of testing.
Pressure pain thresholds (PPTs) were determined for paraspinal muscles overlying bone at following left-sided sites: clavicle site (C5 dermatome) and pancreatic site (T10 BACK (dorsal) dermatome) using a pressure algometer with a 1.0 cm^2 probe (Somedic Sales AB, Horby, Sweden). The clavicle site (the most remote from the pancreatic region) was chosen as reflecting generalized changes in pain processing, that is, supraspinal central sensitization. The pancreatic site was chosen as site reflecting spinal segmental hyperalgesia. These QST techniques in relation to chronic pancreatitis have been described in detail previously.[10]

Statistical analysis
We performed statistical analysis using the Statistica for Windows Software Package (Release 7.0, Statsoft Inc., Tulsa, OK, USA). For all analysis nonparametric tests were used. The clavicle site was compared with the pancreatic site to visualize differences and changes in central spinal and supraspinal central sensitization. Change in pain processing due to bilateral thoracoscopic splanchnicectomy was quantified by calculating the difference between preoperative and postoperative clavicle site or pancreatic site PPT. Patients were divided in two groups based on the direction of changes in clavicle site or pancreatic site PPT due to bilateral thoracoscopic splanchnicectomy: group 'hypoalgesic' was the group which experienced an increase in PPT after bilateral thoracoscopic splanchnicectomy (suggesting a reduction in hyperalgesia with splanchnicectomy) and group 'hyperalgesic' was the group not experiencing such an increase. Analysis for hypoalgesic versus hyperalgesic groups was performed based on both clavicle site and pancreatic site changes in PPT values. Preoperative and postoperative data within the group were compared using a Wilcoxon signed rank sum test; group comparisons (hypoalgesic vs. hyperalgesic for clavicle site and pancreatic site) were done using the Mann-Whitney

U test. To examine the relationships between the NRS change and clavicle site and pancreatic site PPT change perioperatively, we performed non-parametric correlation analysis (Spearman's rank correlation coefficient). Statistical significance was set at $P < 0.05$.

RESULTS

We studied seventeen consecutive patients (10 men and 7 women) with pain and chronic pancreatitis scheduled for thoracoscopic splanchnicectomy. Median age at the time of testing was 47 years (interquartile range (IQR) 45 - 56). Demographic data of the patients are listed in Table 1. All bilateral thoracoscopic splanchnicectomy procedures were technically successful. One patient had a postoperative pneumothorax that was treated with a chest tube. Five patients had postoperative neuralgia in the area of the upper abdomen; this was treated conservatively and diminished in the weeks after operation. These complications are common for this procedure and were mostly transient.

TABLE 1

Demographic and baseline data of the chronic pancreatitis group

	Patients (N = 17)
Age (years)	47 (45 – 56)
Sex ratio - male:female (no.)	10 : 7
Diabetes mellitus (no.)	4
Pancreatic exocrine insufficiency (no.)	4
Etiology (no.)	
Alcohol	6
Other	11
Median NRS*	4 (3 – 6)
Mean onset of chronic pancreatitis (years)	4 (1 – 6)
Regular opioid medication (no.)	17
Morphine equivalents/day (mg)	90 (35 – 133)

All are medians with interquartile ranges unless otherwise specified. Results are demographic details of patients included in this study. 'NRS' is numeric rating scale. *NRSs measured during quantitative sensory testing.

Clinical pain measures

The median preoperative pain NRS of all pancreatitis patients was 4 (IQR 3 - 6). Six weeks after bilateral thoracoscopic splanchnicectomy the median pain NRS was 3 (IQR 0 – 5, $P = 0.097$ vs. preoperatively). No significant difference in preoperative PPT or pain NRS could be found for the hypoalgesic group versus the hyperalgesic groups as based on

clavicle and pancreatic site PPTs. All preoperative and postoperative NRS and PPT are given for hypoalgesic and hyperalgesic group in clavicle site and pancreas site in Table 2. For baseline data only age was significantly different (P = 0.04) between the hyperalgesic and hypoalgesic group for the pancreatic site (Table 3).

TABLE 2

Pain levels and pain scores per group before and after intervention

	Preoperative	Postoperative
PPT clavicle site		
Hypoalgesic	404 (318 – 500)	510 (394 – 568)
Hyperalgesic	468 (363 – 800)	351 (267 – 527)
PPT pancreas site		
Hypoalgesic	508 (345 – 642)	593 (476 – 760)
Hyperalgesic	518 (431 – 626)	396 (309 – 525)
NRS* clavicle site		
Hypoalgesic	4 (3 – 5)	1 (0 – 3)
Hyperalgesic	5 (4 – 6)	6 (5 – 7)
NRS* pancreas site		
Hypoalgesic	5 (4 – 5)	4 (0 – 5)
Hyperalgesic	4 (3 – 6)	2 (0 – 6)

All are medians with interquartile ranges. 'PPT' is pressure pain threshold (kPa) and 'NRS' is numeric rating scale. Clavicle and pancreas are the dermatomes of measurements. Preoperative values were not significantly different between groups. *NRSs measured during quantitative sensory testing.

Clavicle site pressure pain thresholds and pain score

Ten patients (6 men and 4 women) had clavicle site PPT increases after bilateral thoracoscopic splanchnicectomy compared with preoperative values (hypoalgesic group; 87 kPa (IQR 40 - 120), P = 0.0006); in seven patients, clavicle site PPT was unaltered or lower (hyperalgesic group; -135 kPa (IQR -193 – -31), P = 0.003). The postoperative NRS was significantly lower in the clavicle site hypoalgesic group (P = 0.008). The change in NRS was significantly greater in the clavicle site hypoalgesic group versus preoperatively (Figure 1; left: -2 (IQR -4 - 0) vs. 0 (IQR 0 – 1), P = 0.005). The NRS in the hypoalgesic group was significantly reduced with bilateral thoracoscopic splanchnicectomy (P = 0.03), compared with a nonsignificant increase in NRS in the hyperalgesic group (P = 0.1).

TABLE 3

Demographic and baseline data of chronic patients per outcome group

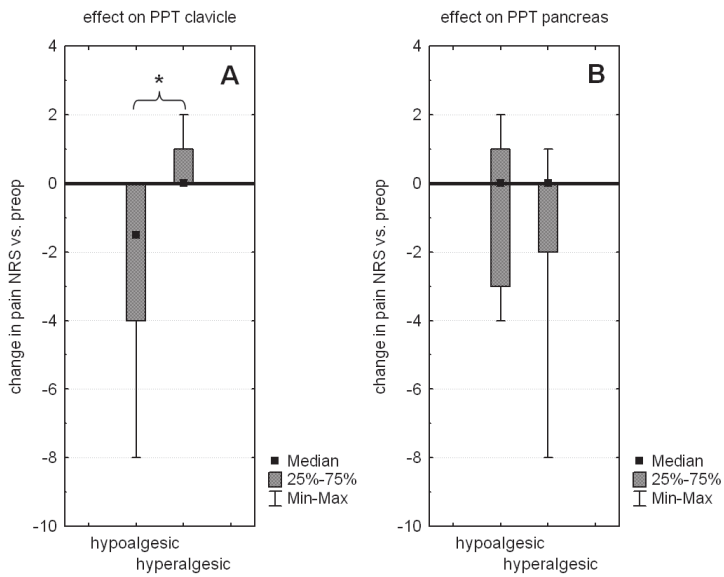
	Hyperalgesic Clavicle (N = 7)	Hypoalgesic Clavicle (N = 10)	P-value	Hyperalgesic Pancreas (N = 11)	Hypoalgesic Pancreas (N = 6)	P-value
Age (years)	31 (41 – 56)	47 (47 – 55)	NS	49 (47 – 57)	45 (36 – 49)	P = 0.04
Sex ratio - male:female - no.	4 : 3	6 : 4	NS	6 : 5	4 : 2	NS
Diabetes mellitus - no.	0	4	NS	2	2	NS
Pancreatic exocrine insufficiency - no.	1	3	NS	4	0	NS
Etiology - no.						
Alcohol	3	3	NS	3	3	NS
Other	4	7	NS	8	3	NS
Mean onset chronic pancreatitis (years)	3 (1 – 5)	4 (1 – 6)	NS	3 (1 – 6)	4 (2 – 5)	NS
Regular opioid medication - no.	7	10	NS	11	6	NS
Morphine equivalents/day (mg)	120 (60 – 131)	50 (28 – 141)	NS	60 (20 – 131)	111 (55 – 240)	NS

Results are demographic details of patients included in this study described per outcome group. All are medians with interquartile ranges unless otherwise specified. 'NS' indicates non-significant.

Pancreatic site pressure pain thresholds and pain score

Regarding pancreatic PPT changes, six patients had an increase (hypoalgesic; 4 men, 2 women; 127 (IQR 86 – 142), P = 0.028), and eleven patients did not (hyperalgesic; 6 men, 5 women; -113 (IQR -132 – -65), P = 0.003). The postoperative NRS was similar in both groups (P = 0.8). The change in pain NRS after bilateral thoracoscopic splanchnicectomy was not significantly greater in the pancreatic hypoalgesic group versus preoperatively (Figure 1; right: 0 (IQR -3 – 1) vs. 0 (IQR -2 – 0), P = 0.5). In neither group was NRS significantly reduced with bilateral thoracoscopic splanchnicectomy (hypoalgesic, P = 0.47 and hyperalgesic, P = 0.11).

FIGURE 1



'NRS' is numeric rating scale and 'PPT' is pressure pain threshold. Values are medians with interquartile ranges (IQR). Box plots of the change in NRSs and change in PPTs after bilateral thoracoscopic splanchnicectomy. Clavicle and pancreas are the dermatomes of measurements. The hypoalgesic group was the group who experienced an increase in PPT after bilateral thoracoscopic splanchnicectomy (suggesting a reduction in preoperative hyperalgesia), and the hyperalgesic group was the group not experiencing such an increase.

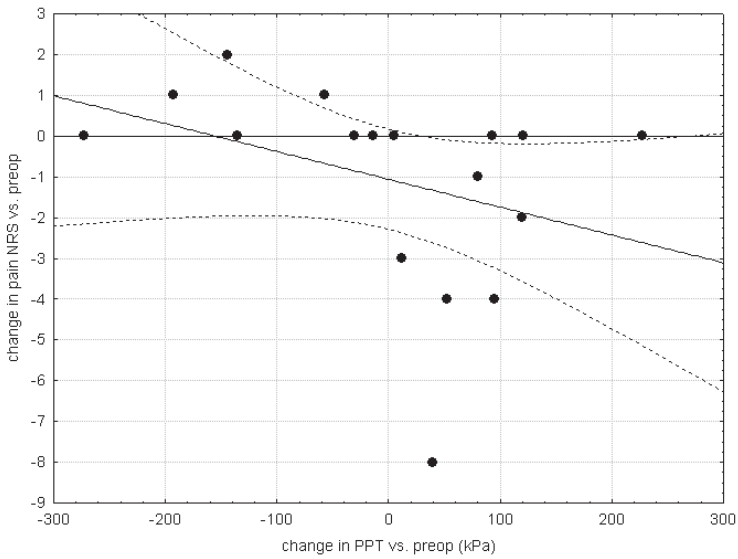
A) The change in NRS after bilateral thoracoscopic splanchnicectomy was significantly greater (marked with an asterisk) in the clavicle site hypoalgesic group versus preoperatively (median -2 (IQR -4 – 0) vs. 0 (IQR 0 – 1), P = 0.005).

B) The change in NRS after bilateral thoracoscopic splanchnicectomy was not significantly greater in the pancreatic hypoalgesic group versus preoperatively (median 0 (IQR -3 – 1) vs. 0 (IQR -2 – 0), P = 0.5).

Correlations between clinical pain measures and quantitative sensory testing

There was a significant negative correlation between the change in NRS and the PPT changes at clavicle site due to bilateral thoracoscopic splanchnicectomy for the group as a whole (rs = 0.53, P < 0.05) (Figure 2). There was no significant correlation between the change in NRS and the PPT changes at the pancreatic site. Also, no significant correlation could be observed between the clavicle site and the pancreatic site PPTs (Table 3).

FIGURE 2



'NRS' is numeric rating scale and 'PPT' is pressure pain threshold. On the y-axis, the change in pain NRS preoperatively versus postoperatively has been mentioned. On the x-axis the change in PPTs preoperatively versus postoperatively in clavicle site has been mentioned. A significant correlation was found between the change in NRS and PPT (rs = 0.53, P < 0.05). This correlation shows that a decrease in pain is correlated with an increase in PPTs. Pressure pain thresholds is in kPa.

DISCUSSION

Only few published studies describe changes in central pain processing in patients with chronic pancreatitis after thoracoscopic splanchnicectomy.[11] We found that an increase in PPTs at the clavicle site after bilateral thoracoscopic splanchnicectomy, distant from the pancreas and thus reflecting supraspinal processing,[10] was associated with a significant reduction in pain scores six weeks postoperatively. This was not the case for the pancreas site, reflecting more segmental spinal processing.[10] In patients in whom bilateral thoracoscopic splanchnicectomy did not show any effect on clavicle site PPT, pain scores were unaltered. These results suggest that in the latter group, central changes in pain

processing might have become independent of ongoing peripheral nociceptive input, resulting in persisting pain despite nociceptive deafferentation via bilateral thoracoscopic splanchnicectomy.[15]

Sensitization of the nervous system is a cardinal feature of most chronic pain disorders.[6] Peripheral nociception at the site of the pancreas can be expected to spread via ascending pathways of the spinal cord to supraspinal structures including the cortex.[12,13] Because of ongoing nociceptive input the dorsal horn of the spinal cord undergoes neuroplastic changes, resulting in an increase in neuronal excitability and, synaptic strength and neuronal reorganization[8], characterized by segmental hyperalgesia at the site of injury.[16] Ultimately ongoing nociceptive drive on secondary neurons will lead to spreading and generalized hyperalgesia, caused by hyperexcitability and firing of supraspinal neurons at lower thresholds.[8] Failure of activation of diffuse noxious inhibitory controls in turn depresses nociceptive activity in dorsal horn neurons; experienced by patients as a reduction in pain.[17,18] All these changes carry the potential of independence from peripheral nociceptive input, where pain and hyperalgesia will then be present even when there is no peripheral nociceptive input.[16]

We found that deafferentation of the pancreas by bilateral thoracoscopic splanchnicectomy did not lead to a decrease in NRS or an increase in distant pain thresholds in a subgroup of pancreatitis patients. Thus, it would appear that we might have identified a subgroup of pancreatic pain patients where supraspinal central sensitization is no longer dependent on peripheral nociceptive input, resulting in absence of pain reduction. This would be the first time this phenomenon has been demonstrated in chronic pancreatitis pain patients, and may explain the relatively large proportion of such patients who fail to respond to typical surgical or pharmacological treatments designed to reduce nociceptive input.[15] Conversely, this study also suggests there is a subgroup of chronic pancreatitis pain patients in whom supraspinal changes in pain processing do depend on peripheral nociceptive input, and in these patients peripheral nociceptive deafferentation via bilateral thoracoscopic splanchnicectomy appears effective in reducing both pain and central sensitization.

Methodological considerations

Alternative explanations for the failure of bilateral thoracoscopic splanchnicectomy to improve hyperalgesia or pain need to be considered. Technical failure due to difficult identification of all the splanchnic branches, variations in morphology, alternative pathways and localization of the greater and lesser splanchnic nerves have all been described in the literature.[13,15] However, during our procedures all nerves and branches were visualized in all patients, and all procedures were classified as technically successful. The surgery of itself could have caused further central sensitization due to nerve destruction resulting

in increased central excitation and facilitation via descending pathways, where finally an autonomous state of chronic pain can be present.[6] However, in our study only a minority of patients showed this phenomenon, and in fact almost two thirds of our chronic pancreatitis patients showed pain reduction due to deafferentation.[4]

Another possible explanation for bilateral thoracoscopic splanchnicectomy failure is that bilateral thoracoscopic splanchnicectomy does not treat the cause of the pain itself, the pancreatitis.[19] Again, however, the question is why this should be true of some pancreatitis patients and not others. An explanation for the difference in pain sensation after the operation by imperfections in the QST protocol is also unlikely. The QST protocol we used is well-standardized and reliable and is generally accepted in the literature as an appropriate and effective method to measure and follow-up pain processing in multiple disorders and patient groups.[10]

In contrast to our previous study we were now able to positively link our QST results (presence or absence of hyperalgesia) to clinical effect.[11] As clinical effect, we used pain scoring by NRS, which is an easy and reliable method of evaluating pain state in patients. In our previous study, success was defined as ceasing opioids within six weeks after the treatment.[11] However, it would have been more appropriate to correlate differences in pain processing, measured by QST, to changes in NRS or VAS, rather than opioid usage, which is influenced by a multitude of factors. Many of these factors are only weakly related to changes in pain processing, which can be expected to occur in the first weeks after nociceptive deafferentation.

An important limitation of this study is the sample size; therefore, important differences in baseline or postoperative measurements could have been missed. Because of the use of a single pain assessment instead of multiple assessments like questionnaires, we may also have missed important outcomes. In this study we only used one modality (mechanical pressure) for the QST, because central sensitization is best reflected by mechanical (e.g. pressure) pain thresholds. Other modalities for example, thermal pain thresholds, mainly reflect peripheral sensitization or nerve damage. Our data might have been different if we used an even more distal site, for example, the trigeminal dermatome, rather than the clavicle site as distant reference site reflecting generalized central sensitization. However, the use of the clavicle site for determining central sensitization has been described before and is more patient friendly.[20]

Clinical implications

This study has shown that there may be groups of patients with chronic pancreatitis that do not benefit from analgesic treatment and surgery that 'deafferents' the pancreas to control pain. It appears important to identify such patients, who are likely to have autonomous changes in supraspinal processing of pain, and might need specific treatment

of central sensitization to control their chronic pain. As suggested in other studies, QST can be used to demonstrate central changes in pain processing and to predict patients that are likely to have no benefit from common therapies modulating nociceptive input such as opioids.[10,21] These data suggest that a local nerve block test (e.g. celiac plexus blockade or differential epidural anesthetic)[22] in combination with a preblockade and postblockade QST before performing a bilateral thoracoscopic splanchnicectomy might be predictive and save these patients an unnecessary surgery, but this needs confirmation by future studies.

Pain control for chronic pain patients resistant to peripheral nociceptive deafferentation can likely be achieved by using medication influencing central changes in pain processing, for example, tricyclic depressants and gabapentinoids.[8,23,24] Interestingly gabapentin has shown to potentiate the effect of opioids in an animal model of pancreatitis.[25] Blockade of the N-methyl-d-aspartic acid receptor, which plays a central role in central sensitization, with ketamine has been proven to be effective in treating central sensitization and hyperalgesia.[6,26] However, more research is needed on the use of ketamine, antidepressants and gabapentinoids in treating therapy resistant chronic pancreatic pain patients.[20]

In summary, pain scores were unaltered in chronic pancreatitis pain patients in whom bilateral thoracoscopic splanchnicectomy did not increase distant PPTs. These results suggest that, in this group, central changes in pain processing might have become independent of ongoing peripheral nociceptive input, resulting in persisting pain despite bilateral thoracoscopic splanchnicectomy. If confirmed in larger studies, these results indicate the importance of sensory testing in the interpretation of unsuccessful interventional pain treatments. Ultimately, the ability to identify patients who have autonomous pain processing will be key to achieving improvements in the management of the disabling pain of chronic pancreatitis patients. More research is needed to achieve greater insight into the alterations of central pain processing accompanying the pain of chronic pancreatitis and thus to treat this pain more effective.

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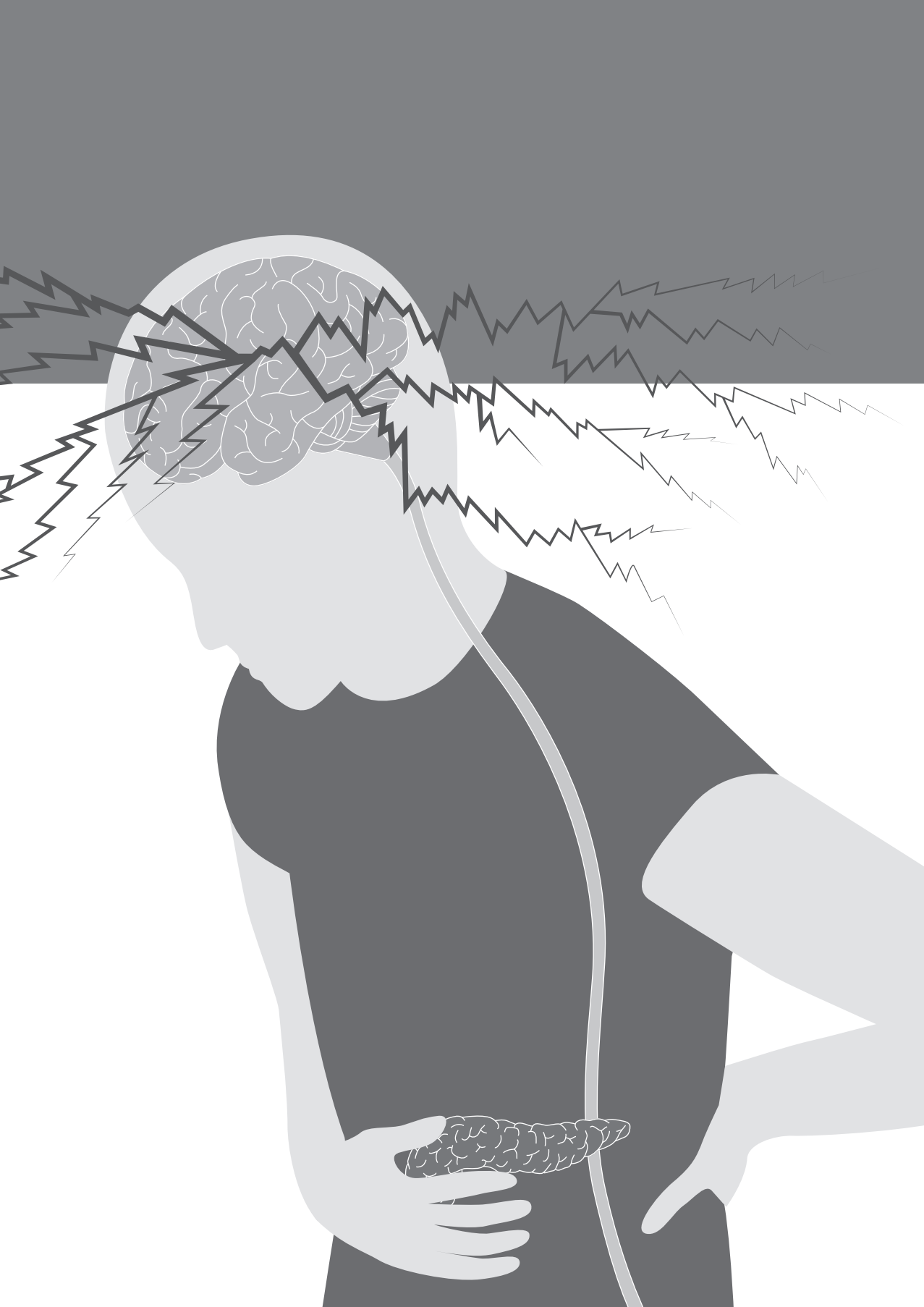

Chapter 6

S-ketamine modulates hyperalgesia in patients with chronic pancreatitis pain

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ABSTRACT

Background and Objectives

Upper abdominal pain is a dominant feature of chronic pancreatitis. A key phenomenon in this context is hyperalgesia, typically associated with N-methyl-D-aspartate (NMDA) receptor activation. This exploratory study evaluates acute effects of S-ketamine, a noncompetitive NMDA antagonist, in modulating generalized hyperalgesia in chronic pancreatitis pain.

Methods

In a blinded crossover trial ten chronic pancreatitis pain patients received S-ketamine for three hours at 2 mcg/kg/min or placebo infusion at an equivalent rate in randomized order. Clinical pain was assessed via visual analog scale (VAS) and short Dutch Language Version McGill Pain Questionnaire (sf-MPQ-DLV). Pressure pain thresholds (PPT) were measured in dermatome C5, T4, T10 BACK (dorsal), L1 and L4, and the sum of PPTs (SOPPT) calculated before, at end of, and after infusion.

Results

Nine patients completed the study. Median pain VAS before infusion was 29 mm at rest, 32 mm during activity; sf-MPQ-DLV score was four. For the S-ketamine session median SOPPT change at infusion end was significantly higher than in the placebo session (218, interquartile range (IQR), 116 - 527 vs. -123 (IQR, -330 – 24), P = 0.005), and significant versus preinfusion values (2109 (IQR, 964 – 3035) vs. 1914 (IQR, 842 – 2884), P = 0.03). SOPPT was unchanged versus preinfusion values and similar between groups one hour after infusion end. No significant changes in VAS and sf-MPQ-DLV occurred.

Conclusions

S-ketamine infusion is more effective than placebo in increasing PPTs in chronic pancreatitis pain patients immediately after infusion. This effect did not outlast the infusion. Further research is warranted into S-ketamine use for reducing generalized hyperalgesia and chronic pancreatitis pain.

INTRODUCTION

Chronic pancreatitis involves progressive inflammatory changes in the pancreas that damage its structure, leading to exocrine and endocrine dysfunction.[1] In western countries, alcohol is the main cause of chronic pancreatitis. Upper abdominal pain, present in 80 - 90% of patients, is a dominant feature and the best predictor for health-related quality of life.[2] The relapsing painful attacks and severe pain accompanying chronic pancreatitis remains a major therapeutic challenge, often leading to opioid dependence, recurrent hospitalization, and medical interventions.[3]

The intense visceral nociception in chronic pancreatitis due to inflammation, nerve damage or elevated intrapancreatic pressure leads to relapsing painful attacks and often continuous pain.[4] This often leads to central nervous system reorganization and sensitization, whose presence has been demonstrated using quantitative sensory testing (QST) and electroencephalography.[5,6] Central sensitization increasess excitability of central nervous system nociceptive neurons amplifying signals coming from the periphery, manifest as generalized hyperalgesia.[7] Another cause of hyperalgesia in pancreatitis may be opioid-induced hyperalgesia.[8]

A key mechanism in central sensitization and opioid-induced hyperalgesia is that of activation of N-methyl-D-aspartate (NMDA) receptors.[9] S-ketamine is a non-competitive NMDA receptor antagonist.[10] Multiple studies have consistently produced positive results regarding the use of S-ketamine in (chronic) pain patients with central sensitization and hyperalgesia.[11] We therefore hypothesize that S-ketamine, with its ability to depress central nociceptive sensitization and opioid-induced hyperalgesia, will positively affect the generalized hyperalgesia present in chronic pancreatitis patients.[5] At the moment there are no formal studies on the use of S-ketamine for this purpose.

The aim of this hypothesis-generating exploratory study is to investigate the effects of S-ketamine infusion on the generalized hyperalgesia present in chronic pancreatitis patients on stable opioid therapy using somatic QST.

METHODS

Study patients

The institutional medical Ethics Committee approved the protocol. All patients gave written consent. Patients were eligible if they were at least eighteen years of age, had chronic pancreatitis pain, had active but clinically stable chronic pancreatitis, and were on stable opioid therapy. Patients had no surgically treatable anatomic substrate for chronic pancreatitis pain. Patients with a psychiatric disorder or encephalopathy, sufficient to compromise data collection for example QST, were excluded. The patients' medical and demographic data were obtained from the patient records. Opioid medication for each

patient was converted to morphine equivalents per day using the Narcotic Analgesic Converter (version 2.0, GlobalRPh! Inc.; www.GlobalRPh.com).
To confirm the presence of generalized hyperalgesia at baseline in the pancreatitis patients, an age and sex matched normal values group consisting of nine patients without a painful condition scheduled for routine gynecologic or urologic elective surgery was chosen for comparison from our hospital QST database.

Study drug
S-ketamine (Ketanest-S, Pfizer, Capelle a/d IJssel, the Netherlands) was supplied to the nursing ward by the anesthesiology department. A dosage of 2 mcg/kg/min of S-ketamine is comparable with a dosage of 4 mcg/kg/min for racemic ketamine. The blinded syringes contained either a solution of 20 ml of S-ketamine with a concentration of 2.5 mg/ml or 20 ml of NaCl 0.9% as placebo. Experienced doctors administered all study drugs.

Clinical pain assessment
Mean pain and worst pain was scored by means of a visual analog scale (VAS; 0 mm represented no pain and 100 mm represented unbearable pain) at rest, during activity and during eating (only preinfusion). The short Dutch Language Version of the McGill Pain Questionnaire – sf-MPQ-DLV – was used to determine intensity and emotional impact of pain at rest. The sf-MPQ-DLV contains eleven items for assessing sensory dimensions of pain and four items for affective dimensions of pain. Only the sum of values for sensory and affective dimensions was used in the analysis.

Quantitative sensory testing
Quantitative sensory testing took place using a standard temporal test sequence. Testing in females was not standardized with regard to phase of the menstrual cycle because all were amenorrheic postmenopausal. Pressure pain tolerance thresholds were tested using a pressure algometer with a 1.0 cm^2 probe (Somedic Sales AB, Horby, Sweden), at the following sites on the dominant body side: lower neck (C5 dermatome), sternum (T4 dermatome), pancreatic site (T10 BACK (dorsal) dermatome), hip region (L1 dermatome) and knee (L4 dermatome). The sum of pressure pain threshold (SOPPT) was chosen for evaluation of generalized hyperalgesia as a simple method of including all dermatomes, thus reflecting total body hyperalgesia.

Study design
This was a blinded and placebo-controlled crossover trial that evaluated the influence of S-ketamine on generalized hyperalgesia in patients with chronic pancreatitis at one hospital in the Netherlands. Sealed envelopes were used for randomization and were

opened after data lock. Eligible patients randomly received placebo or S-ketamine on the first visit and at least one week later the opposite regimen during the second visit. During both sessions, at the same time of the day, patients received infusion for three hours at a rate equivalent to S-ketamine 2 mcg/kg/min or placebo. During the visits patients were only allowed to drink clear fluids without sugar. Before infusion was started, QST was performed, pain experience was measured by the sf-MPQ-DLV and pain intensity by a VAS score. This was repeated immediately after three hours of infusion and one hour after the end of infusion. Side effects and hemodynamic parameters were monitored.

Efficacy end points

The primary study endpoint was the difference in change versus before infusion values of SOPPT. This was compared for immediately after, or one hour after the end of, the three hour infusion for the S-ketamine versus placebo group.

Secondary endpoints

1) Differences in the change versus baseline PPT values in the individual dermatomes before and after S-ketamine versus placebo infusion; 2) changes in subjective pain sensation measured by VAS scores (at rest or during activity) for S-ketamine versus placebo immediately after and one hour after the end of drug infusion; 3) (changes in) the sf-MPQ-DLV for S-ketamine versus placebo at the same time points; and 4) the observed adverse effects during study drug infusion.

Statistical analysis

We performed statistical analysis using Statistica (release 7.0, Statsoft Inc, Tulsa, Okla). Statistical significance was set at $P \leq 0.05$. We used Mann-Whitney U test to analyze: 1) generalized hyperalgesia by comparing the before infusion SOPPT of the normal values group and study group; 2) the change in SOPPT between the S-ketamine and placebo sessions immediately after and one hour after infusion; 3) before infusion differences in primary and secondary endpoints regarding study session (i.e. placebo vs. S-ketamine) and gender; and 4) differences in secondary endpoints for placebo versus S-ketamine immediately after and one hour after infusion. A Wilcoxon signed rank-test was performed to determine the difference between SOPPT, VAS and sf-MPQ-DLV scores before versus immediately after infusion or before versus one hour after infusion for the placebo and S-ketamine sessions. The relationship between QST results and VAS scores was examined with a Spearman's rank correlation coefficient.

RESULTS

Study population

Ten patients were randomized; the study was completed without any incident. One patient dropped out of the study after randomization for personal reasons. All patients (5 women, 4 men; mean age 53.2 ± 5.7 years) had pain due to chronic pancreatitis and were on a stable opioid therapy. Their median opioid consumption was 160 (interquartile range (IQR) 160 – 315) mg of morphine equivalents per day. Their median VAS scores before infusion were 29 (IQR 14 – 48) mm at rest and 32 (IQR 23 – 68) mm during activity. The median score of the sf-MPQ-DLV before infusion was four (IQR 2 – 6). More demographic data of the study population and normal values group are listed in Table 1.

TABLE 1

Demographic and baseline data of the chronic pancreatitis group

	Pancreatitis (N = 9)	Normal values (N = 9)
Age (years)	52 (50 – 58)	52 (47 – 55)
Sex ratio, male:female	4 : 5	4 : 5
Diabetes mellitus	3	-
Pancreatic exocrine insufficiency	0	-
Previous abdominal surgery	5	-
Frey procedure	1	-
Partington-Rochelle procedure	1	-
Whipple procedure	1	-
Stent placement	1	-
Pancreas tail resection	1	-
Etiology		
Alcohol	6	-
Hypertriglyceridemia	1	-
Unknown	2	-
PPT (dermatome), kPa		
C5	229 (198 – 533)	574 (470 – 740)
T4	280 (219 – 490)	602 (473 – 827)
L1	352 (179 – 564)	502 (417 – 576)
T10 dorsal	341 (275 – 568)	666 (446 – 887)
L4	355 (298 – 740)	735 (485 – 875)

Results are medians with interquartile ranges unless otherwise specified.

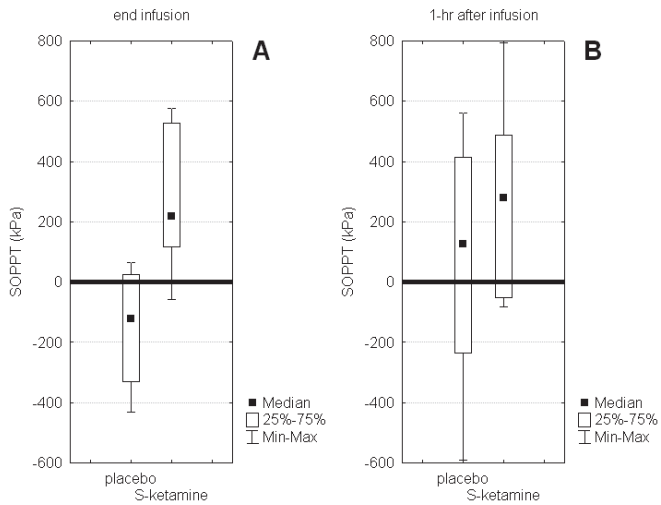
Baseline pain pressure thresholds

A significant difference was found in baseline measurements for SOPPT between the normal values group (9 patients) 2900 kPa (IQR 2349 - 3461) and the chronic pancreatitis group 1583 kPa (IQR 1221 - 3191), P = 0.04. More patient baseline PPT measurements are listed in Table 1. Before infusion, PPTs did not differ significantly between visits or sex.

Immediately after end of infusion

The change in SOPPT was significantly higher in the S-ketamine session immediately after the end of infusion as compared to the placebo session 218 kPa (IQR 116 – 527) versus -123 kPa (IQR -330 – 24), P = 0.005 (Figure 1A). Only in the S-ketamine session were SOPPT values immediately after end of infusion significantly higher than pre-infusion 2109 kPa (IQR 964 – 3035) versus 1914 kPa (IQR 842 – 2884), P = 0.03. A significantly more positive change in PPT was observed in dermatomes L1 and L4 in the S-ketamine versus placebo group immediately after the infusion end 121 kPa (IQR 1 - 254) versus -21 kPa (IQR -97 – 25), P = 0.04; and 107 kPa (IQR 68 – 148) versus -20 kPa (IQR, -97 – -3), P = 0.01; respectively; with the differences for the other dermatomes not reaching significance (Figure 2).

FIGURE 1

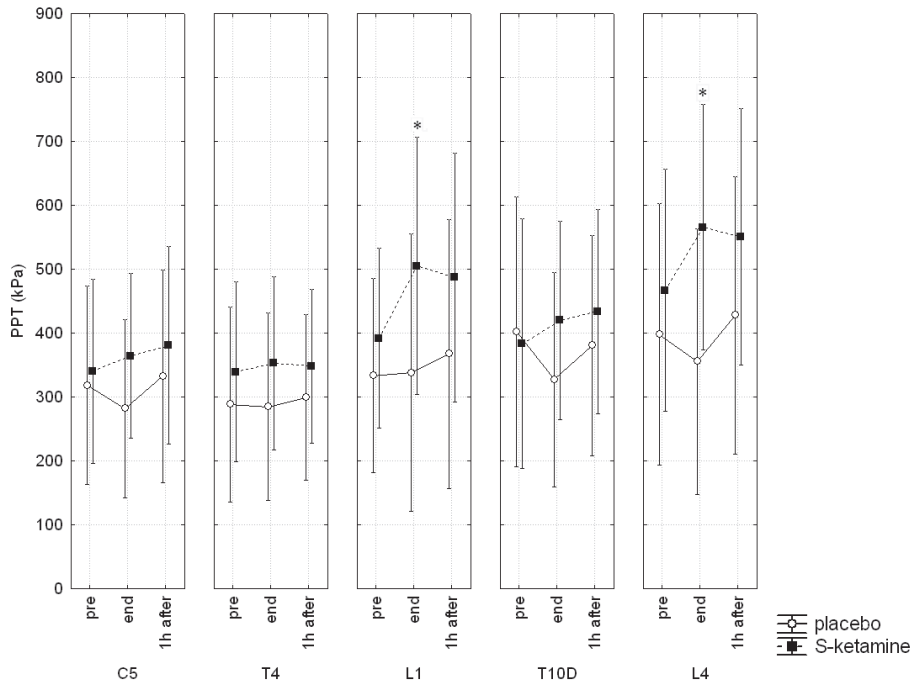


'SOPPT' is sum of pressure pain thresholds. Values are medians with interquartile ranges (IQR) and plotted in a box plot.
A) The change in SOPPT immediately after the end of infusion versus pre-infusion of the trial medication compared for the placebo and S-ketamine groups. The placebo group has a median of -123 kPa (IQR -330 – -24), and the S-ketamine group has a median of 218 kPa (IQR 116 – 527).
B) The change in SOPPT versus pre-infusion one hour after the end of infusion of the trial medication compared for the placebo and S-ketamine groups. The placebo group has a median of 127 kPa (IQR -235 – 415) and the S-ketamine group has a median of 280 kPa (IQR -51 – 489).

One hour after end of infusion

One hour after end of infusion, there were no statistically significant differences between sessions for PPT (Figure 1B). Furthermore, SOPPT at one hour after infusion end was not higher than before infusion values in either session.

FIGURE 2



All measurements for pressure pain thresholds (PPT) in kPa for all five dermatomes pre-infusion, immediately after the end of infusion, and one hour after infusion end of the trial medication are compared for placebo and S-ketamine groups. Results are medians with interquartile ranges. 'T10D' is T10 BACK (dorsal). Differences marked with an asterisk are statistically significant.

VAS scores and sf-MPQ-DLV

Neither session (S-ketamine vs. placebo) nor sex significantly influenced pain VAS scores at rest and during activity or sf-MPQ-DLV results before infusion. The only exception was that maximum pain during eating was significantly higher for men (P = 0.016).

Changes in VAS scores at rest and with activity and sf-MPQ-DLV immediately and one hour after infusion end were similar for both treatment sessions. Furthermore there were no significant changes in VAS and sf-MPQ-DLV scores within the sessions immediately after or one hour after infusion end as compared with before infusion. However, there was a significant difference for the sf-MPQ-DLV sensory scores of the placebo group pre- and immediately after infusion end (P = 0.018).

No significant correlations between VAS scores, sf-MPQ-DLV scores and the SOPPT were found before, immediately after and one hour after infusion end, for both sessions taken together or taken separately.

Adverse effects

Adverse effects during infusion with S-ketamine were categorized as light and were no reason to stop the experiment. Light-headedness was reported by four patients and disappeared after the infusion ended. One patient felt dizzy at the end of infusion with stable hemodynamic values. Another patient mentioned an odd taste that also disappeared after stopping the infusion. No side effects were reported during the infusion with placebo.

DISCUSSION

Current treatment concepts for pancreatic pain increasingly target control of hyperalgesia by using tricyclic antidepressants, gabapentin, or pregabalin.[12] Opioids initially provide analgesia to chronic pancreatitis patients, but have considerable adverse effects. Indeed, opioid usage may induce and maintain hyperalgesia and thus become a part of this painful condition.[8] Our patients had significantly lower pre-infusion SOPPT for all dermatomes versus normal values, compatible with generalized hyperalgesia. Ours is the first study to analyze (acute) antihyperalgesic effects of infusion with S-ketamine in chronic pancreatitis patients. The study demonstrates the tolerability and short-term effect of S-ketamine in the acute treatment of generalized hyperalgesia accompanying the pain of chronic pancreatitis. Further studies are necessary to determine optimum indications, treatment paradigms and long-term effects of S-ketamine in this context.

Hyperalgesia and ketamine

Chronic pain is increasingly recognized to be characterized by altered pain processing, including spreading (or generalized) hyperalgesia and pronociceptive pain modulation.[13,14] This is also the case for chronic pancreatitis where neuroplastic changes at spinal and supraspinal sites due to chronic nociceptive input are increasingly being demonstrated.[12] Ongoing nociceptive input will ultimately lead to central sensitization and loss of descending inhibitory control mechanisms that may end in an autonomous pain state.[15] In our study we observed a significant increase in SOPPT with S-ketamine treatment, suggesting that S-ketamine may be successful in acutely treating the generalized hyperalgesia associated with chronic pancreatitis pain.[5,16] This result is compatible with others demonstrating antihyperalgesic actions of S-ketamine on central sensitization and chronic pain.[17,18] After the end of S-ketamine infusion the QST changes disappeared rapidly. This may be related to the relatively short infusion period and the low dosage chosen. Studies with infusion periods up to days show a more prolonged effect with ketamine.[19] But long-term and high-dose ketamine therapy may have neurotoxic effects, as described in animal studies,[19,20] but is unstudied in humans. Available human

data suggest that low ketamine infusions of up to seven days are without long-term deleterious effects.[21] Unfortunately, studies describing other routes, for example oral or subcutaneous, have shown limited and unpredictable clinical effects.[22,23] Clearly, further studies are needed to resolve these issues.

Methodological considerations

This small hypothesis-generating exploratory study focused on the acute effect of S-ketamine on hyperalgesia. A limitation of this study is the short time of infusion and lack of longterm follow-up. Thus we could have missed a delayed antihyperalgesic effect of S-ketamine infusion in reducing later pain scores and perhaps opioid consumption. Future studies should include more patients and document the long-term effects of S-ketamine infusion. Alternative application routes (e.g. oral and intranasal) or other forms of NMDA receptor blockade (e.g. memantine and amantadine) are interesting alternatives. A control group of healthy subjects was not included in the trial for the evaluation of the effect of S-ketamine for the simple reason that assessment of antihyperalgesic efficacy requires the presence of hyperalgesia – and this is not present in healthy subjects. QST provides objective and quantifiable data on pain processing and is a valuable tool for observing processes and mechanisms underlying chronic pain and its treatment.[5,24] In contrast to VAS, QST measures an aspect of pain, sensory discrimination. SOPPT change immediately after S-ketamine infusion was not accompanied by significant changes in VAS and MPQ scores. However, numerous studies have shown weak relationships between VAS and QST.[5]

Conclusions and summary

Our study provides preliminary evidence that administration of S-ketamine may be more effective than placebo treatment in increasing PPT in patients with hyperalgesic painful chronic pancreatitis. However, this effect is limited to the period of infusion, and no improvement was seen in accompanying pain scores. The adverse effects reported in the S-ketamine group were transient and mild. More research is needed regarding the long-term effects of infusion, dosage schemes and the relevance of the short-lasting elevation of pain thresholds.

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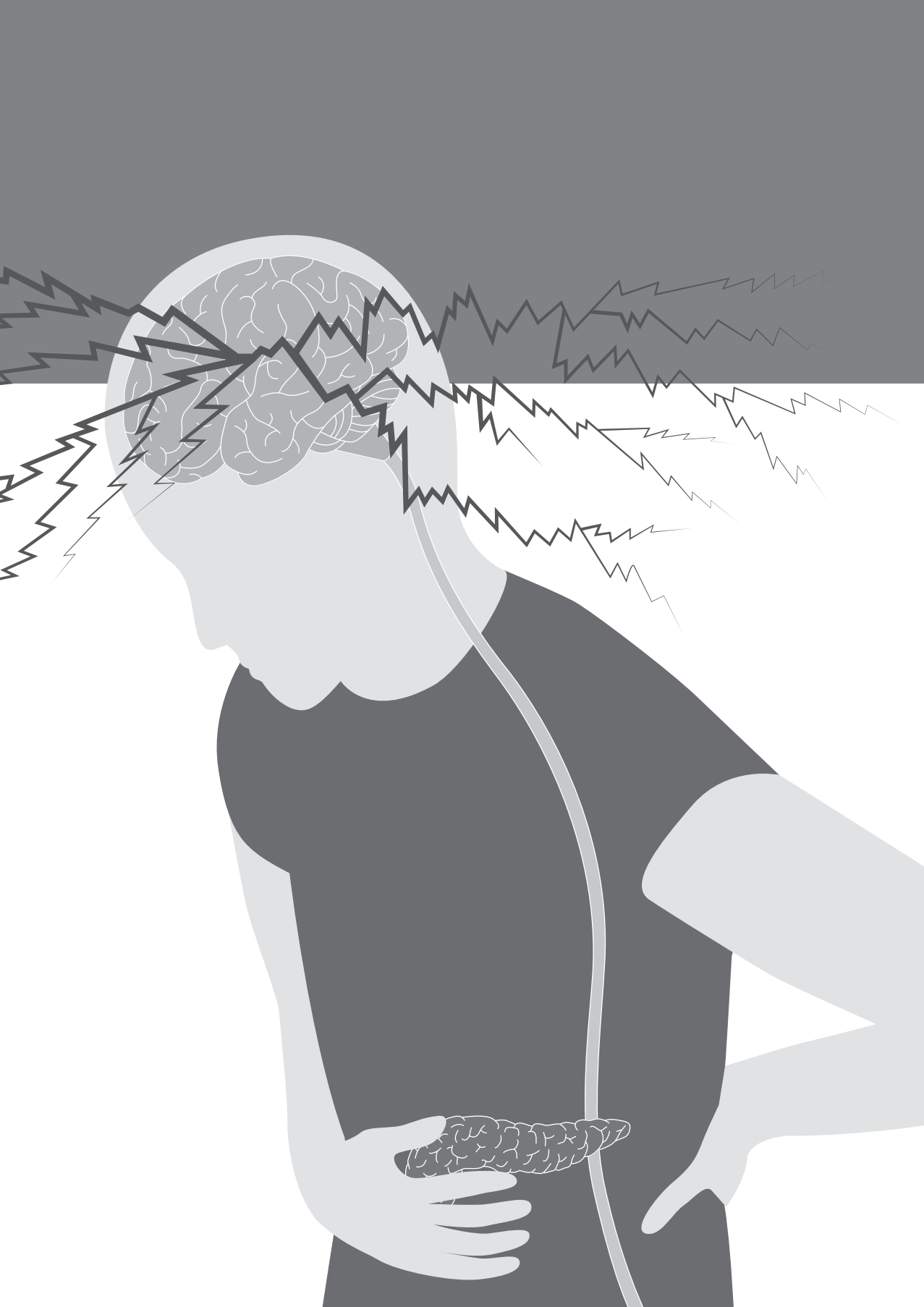

Chapter 7

Pregabalin reduces pain in patients with chronic pancreatitis in a randomized, controlled trial

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ABSTRACT

Background & aims

Pain is a disabling symptom for patients with chronic pancreatitis and difficult to treat. Evidence from basic science and human studies indicates that pain processing by the central nervous system is abnormal and resembles that observed in patients with neuropathic pain disorders. We investigated whether agents used to treat patients with neuropathic pain are effective in chronic pancreatitis.

Methods

We conducted a randomized, double-blind, placebo-controlled trial to evaluate the effects of pregabalin as an adjuvant analgesic. We measured pain relief, health status, quality of life and tolerability in 64 patients with pain from chronic pancreatitis; they were randomly assigned to groups given increasing doses of pregabalin or placebo (control) for three consecutive weeks. The primary endpoint was pain relief, based on a visual analogue scale documented by a pain diary. Secondary endpoints included patients' global impression of change (PGIC) score, changes in physical and functional scales, pain character, quality of life, and tolerability.

Results

Pregabalin, compared with placebo, caused more effective pain relief after three weeks of treatment (36% vs. 24%; mean difference, 12%; 95% confidence interval, 22% - 2%, P = 0.02). The percentage of patients with much or very much improved health status (PGIC score) at the end of the study was higher in the pregabalin than the control group (44% vs. 21%, P = 0.048). Changes in physical and functional scales, pain character, and quality of life, and number of serious adverse events were comparable between the groups.

Conclusions

In a placebo-controlled trial, pregabalin is an effective adjuvant therapy for pain in patients with chronic pancreatitis.

INTRODUCTION

Upper abdominal pain is a dominant feature of chronic pancreatitis, and its treatment remains a major clinical challenge.[1] Analgesic medication is part of the initial treatment and often includes opioids in the absence of pathology suitable for endoscopic or surgical interventions.[2] However, opioid-based analgesia often only shows limited effectiveness in these patients and is frequently accompanied by undesirable side effects.[3]

Basic studies of pancreatic nerves and experimental human pain research have provided evidence that pain processing is abnormal in patients with chronic pancreatitis and in many patients resembles that seen in neuropathic pain disorders.[4-7] Gabapentinoids, including pregabalin, have effectively been used to treat various neuropathic pain disorders, including diabetic neuropathy, postherpetic neuralgia, and neuropathic pain of central origin.[8-13]

Based on the limited effectiveness of conventional opioid-based analgesic approaches to chronic pancreatitis pain, and the finding that pancreatitis pain is accompanied by similar alterations of central pain processing as seen in neuropathic pain, we hypothesized that pregabalin could be effective as an adjuvant treatment to decrease pain associated with chronic pancreatitis. The aims of this study were to evaluate the effects of pregabalin on pain relief, health status, and quality of life, and to understand the tolerability in patients with chronic pancreatitis.

PATIENTS AND METHODS

Study oversight

The study was an investigator initiated, double-blind, placebo-controlled, parallel-group study of increasing doses of pregabalin conducted in the Netherlands and Denmark. Pfizer donated pregabalin and identical capsules containing placebo but was not involved in study design, accrual, or analyses of data. The study was approved by the responsible Ethical Committees and medical agencies in both countries, and all patients provided written informed consent. The study is registered with ClinicalTrials.gov (NCT 00755573).

Patients

Inclusion criteria were a diagnosis of chronic pancreatitis based on the Mayo Clinic diagnostic criteria and chronic abdominal pain typical for pancreatitis (i.e. dull epigastric pain more than three days per week for at least three months).[14] Patients taking concomitant analgesic medication and expected to stay on a stable regime during the trial were allowed to enter the study. Key exclusion criteria for patients were generalized painful conditions other than chronic pancreatitis, pregnancy or lactation, active (or history of) major depression, moderate to severe renal impairment, an abnormal electrocardiogram at screening, and hypersensitivity to pregabalin or any of it components.

Randomization and blinding

Patients meeting eligibility criteria were randomly assigned in a one to one ratio to receive either pregabalin or placebo. Randomization blocks had a size of six and were computer generated by a pseudo-random code. Trial participants were stratified according to absence or presence of diabetes mellitus; no other actions were taken to match the groups. Patients and those administrating study medication, assessing outcomes, and analyzing data were blinded to group assignment.

Outcomes

The primary endpoint was change in pain intensity after three weeks of study treatment versus baseline pain intensity recorded for one week prior to start of medication. Average and maximum daily pain intensities were recorded using a pain diary based on a visual analogue scale (VAS) where 0 = no pain and 10 = worst pain imaginable. Secondary efficacy parameters were patients' global impression of change (PGIC) score at the end of the study period[15] and changes in modified Brief Pain Inventory-Short Form (BPI) questionnaire scores.[16] The BPI is a 14-item questionnaire that asks patients to rate pain during the prior week and the degree to which it interferes with daily activities on a 0 to 10 scale. It can be summarized in a pain composite score and an interference composite score.[16,17] Furthermore, changes in quality of life assessed by the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30) and tolerability of pregabalin compared to placebo were considered as secondary end points.[18] Changes in as needed opioid analgesics (morphine equivalents per day) and body mass index were collected as exploratory end points.

Procedures

Screening procedures included a detailed patient history to determine pain localization and characteristics. To complement pain characterization, the Pain Detect Questionnaire (PDQ) was collected. This constitutes a simple screening tool to predict the likelihood of a neuropathic pain component being present in individual patients.[19] Patients` pain medication history was documented in detail, including amount and frequency of any analgesics. Also, a physical examination, including measurement of weight, height, full blood count, urea, electrolytes, liver function tests, and electrocardiography was performed at the screening visit. Eligible patients completed the BPI and QLQ-C30 questionnaires and were trained in the use of the pain diary. Patients returned for an enrollment visit one week after screening. During this visit, pain diaries were reviewed to ensure correct registration of baseline pain scores, information on analgesics was reassessed, and patients were instructed in proper administration and adjustment of the study medication. All patients received their initial dose of study drug and were monitored for 60 minutes for adverse events.

During the study period, patients received increasing doses of either pregabalin or matching placebo. Initial dose was 75 mg pregabalin twice daily. After three days this was increased to 150 mg pregabalin twice daily, with a further increase to 300 mg twice daily after one week and for the rest of the study period. An equivalent regime was followed in the placebo arm. All patients followed the same oral dosing schedule. Daily dosages were split into two equivalent doses, one administered in the morning between 7.00 a.m. and 10.00 a.m. and one in the evening between 7.00 p.m. and 10.00 p.m. If unacceptable side effects were experienced by the patient, a single downward dose titration was allowed, with the patient staying on that final dosage for the remaining study period. Telephone interviews were scheduled at four, seven, eleven, fourteen, and seventeen days to assess the presence, severity, and tolerability of adverse events. These were collected based on their occurrence and documented in individual case report forms. After completion of the three weeks study period, patients were seen for a final visit, which included change in measurements as described for screening and the PGIC questionnaire. At the final visit patients were instructed to taper their study medication by halving their dose for seven days and then to stop medication.
Patients were told to return surplus study medication. Any discrepancy in the number of pills returned from the expected number of pills to be used was noted in the patient's case report form. Compliance was calculated as this discrepancy divided by the number of pills expected to be used by the individual patient.

Statistical analysis

The study was powered to detect a difference in average daily pain scores of 25% between groups during the three weeks of study treatment. On the basis of an assumed baseline average pain score of four and a standard deviation (SD) of 30%, we determined that a study with 30 patients per group was needed to provide a power of 90% with the use of a two-sided significance level of 0.05. Hence, the sample size was set at 64 patients to allow for possible dropouts.
All data were analyzed according to the intention-to-treat principle. Data are presented as means with standard deviations unless otherwise indicated. Pain diary data were baseline corrected to offset individual differences in baseline pain scores. The retrieved changes were transformed to a relative scale (%) and subjected to analysis of variance with the factors study treatment (pregabalin vs. placebo) and study days (days 1 - 21) and the interaction of these factors. Wald tests were used for post hoc analysis. Changes in tabulated data were given as risk ratios and compared by a Chi-square test or Fisher's exact test as appropriate. To examine the correlation between change in diary pain score and PGIC, we used the Pearson correlation coefficient. Changes in BPI scores, QLQ-C30 scales or items, as needed opioid analgesics, body mass index, and compliance were compared

by Student t-test or Mann-Whitney U test as appropriate. The software package Stata/IC version 11.1 (StataCorp LP, College Station, Tx) was used for the statistical analyses.

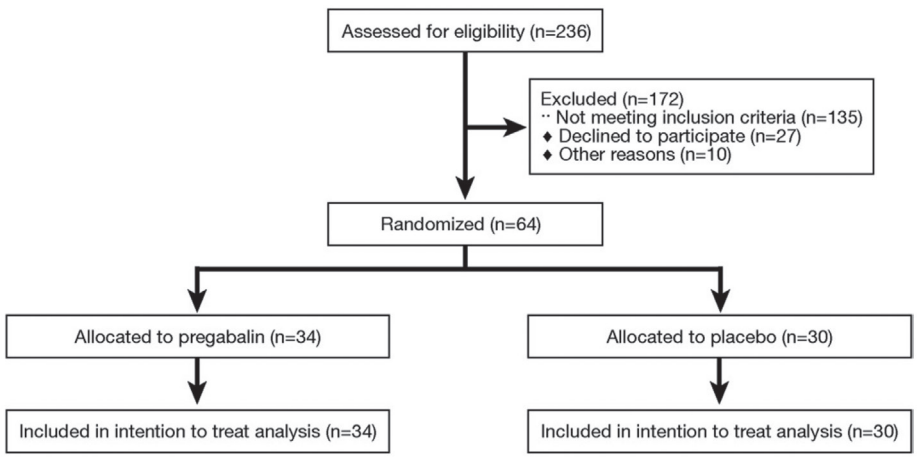
RESULTS

Enrollment, baseline characteristics, and study treatments

From October 2008 to May 2010, a total of 236 patients were screened and 64 underwent randomization (Figure 1). The study was terminated as planned after randomization of 64 patients. The two treatment groups were comparable with respect to demographic characteristics, clinical data, and baseline pain scores (Table 1). In the pregabalin group, 20 patients (61%) tolerated a final dose of 600 mg pregabalin; in the placebo group, 26 patients (90%) tolerated the maximal placebo dose (P = 0.01).

FIGURE 1

Study enrollment and randomization



Outcomes

Changes in primary and secondary endpoints are summarized in Table 2. For the whole treatment period, an overall difference in change of average pain score between pregabalin- and placebo-treated patients was evident (F = 8.8, P = 0.003). Post hoc analysis revealed a significant difference in pain reduction after three weeks of study treatment (36% vs. 24%; mean difference, 12%; 95% confidence interval (CI), 22% to 2%, P = 0.02) (Figure 2). In addition, an overall difference in change of maximal pain scores was seen for the whole treatment period (F = 8.9, P = 0.003), with a significant

difference between groups after three weeks (32% vs. 22%; mean difference, 10%; 95% CI, 19% to 2%, P = 0.02).

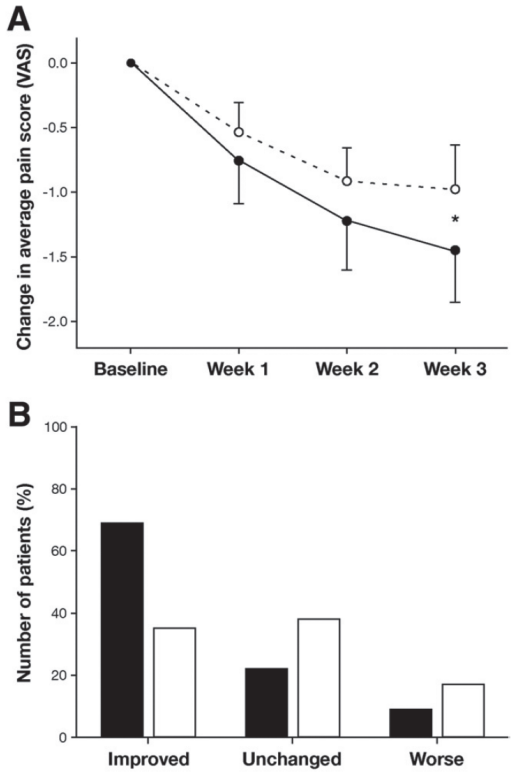
TABLE 1

Demographic and clinical characteristics of patients at randomization

	Pregabalin (N = 34)	Placebo (N = 30)
Age (years)	52 ± 10	55 ± 12
Males – no. (%)	21 (62)	19 (63)
Etiology – no. (%)		
Toxic-metabolic	16 (47)	17 (57)
Idiopathic	11 (32)	11 (37)
Genetic	2 (6)	0 (0)
Autoimmune	1 (3)	0 (0)
Recurrent and severe acute pancreatitis	2 (6)	1 (3)
Obstructive	2 (6)	1 (3)
Diary pain score (visual analogue scale 0-10)		
Average pain	4.2 ± 2.2	3.9 ± 2.2
Maximal pain	5.8 ± 2.3	5.2 ± 2.3
BPI		
Pain score	4.4 ± 2.2	4.1 ± 2.1
Interference score	4.7 ± 2.1	4.6 ± 1.7
PDQ – no. (%)		
Neuropathy unlikely	19 (56)	10 (33)
Neuropathy possible/likely	15 (44)	20 (67)
Concomitant analgesics – no. (%)[a]		
None	3 (9)	2 (7)
Weak analgesics	7 (21)	11 (37)
Strong analgesics	24 (71)	17 (57)
Duration of chronic pancreatitis (months)	103 ± 75	111 ± 83
Diabetes mellitus – no. (%)	10 (29)	10 (33)
Previous interventions for chronic pancreatitis – no. (%)		
Pancreas resection/drainage procedures	6 (18)	5 (17)
Thoracoscopic splanchnic denervation	2 (6)	4 (13)
Celiac blockade	1 (3)	1 (3)
Patients treated with enzymes for pancreatic exocrine insufficiency – no. (%)	18 (53)	13 (43)
Ongoing alcohol abuse – no. (%)[b]	7 (21)	11 (37)
Current smoker – no. (%)	26 (76)	22 (73)
Body mass index (kg/m2)	22.2 ± 5.7	22.5 ± 3.1

Values are means with standard deviations. 'BPI' denotes Brief Pain Inventory Short Form and 'PDQ' denotes Pain Detect Questionnaire. Percentages may not total 100 due to rounding.
[a]Weak analgesics were defined as NSAIDS, paracetamol, codeine and tramadol. Strong analgesics were defined as opioid-based therapies. [b]Alcohol abusing patients were defined as female patients drinking > 14 units of alcohol per week or male patients drinking > 21 units of alcohol per week.

Figure 2
Primary and secondary outcomes



A) Changes in average pain score on a visual analogue scale (VAS). The *black circles* and *solid line* represent pregabalin-treated patients, and the *white circles* and *dashed line* represent patients receiving placebo. Bars are standard errors. P = 0.02 comparing pregabalin and placebo.
B) PGIC at the end of the study. *Black bars* represent pregabalin-treated patients, and *white bars* represent patients receiving placebo. There was a better treatment response in the pregabalin group (P = 0.048).

More patients rated their treatment response (PGIC) as much or very much improved in the pregabalin group (44%) compared with the placebo group (21%) (P = 0.048). The changes in average pain diary scores were correlated with PGIC scores for both the pregabalin group (r = 0.7, P < 0.001) and placebo group (r = 0.5, P = 0.002). No differences between treatments were seen for the BPI composite scores.

Changes in QLQ-C30 subscales and items are summarized in Table 3. An increase in quality of life of 9.7 points was observed in the pregabalin group compared to a decrease of 1.7 points in the placebo group (P = 0.12). No differences were seen for any of the other QLQ-C30 subscales or items.

TABLE 2

Changes in primary and secondary endpoints after three weeks of study treatment

Variable	Pregabalin (N = 34)	Placebo (N = 30)	Pregabalin vs. placebo	P-value
Average diary pain score	-36% (-43%- -29%)	-24% (-31%- -16%)	-12% (-22%- -2%)	0.02
Maximal diary pain score	-32% (-38%- -26%)	-22% (-28%- -16%)	-10% (-19%- -2%)	0.02
PGIC				0.048
Very much improved	1 (3)	2 (7)		
Much improved	13 (41)	4 (14)		
Minimally improved	8 (25)	7 (24)		
No change	7 (22)	11 (38)		
Minimal worse	0 (0)	4 (14)		
Much worse	2 (6)	1 (3)		
Very much worse	1 (3)	0 (0)		
BPI				
Pain score	-1.2 (-2.2- -0.2)	-0.4 (-1.1- -0.4)	-0.8 (-2.0- -0.4)	0.19
Interference score	-1.3 (-2.2- -0.3)	-1.0 (-1.7- -0.2)	-0.3 (-1.5- -0.9)	0.61

Pain diary data were available for 33 patients (97%) in the pregabalin group and 29 patients (97%) in the placebo group; two patients in the pregabalin group left the study after eleven days and eighteen days; their data were included until then. Patients' Global Impression of Change (PGIC) and Brief Pain Inventory-short Form (BPI) were available for 29 patients (97%) in the placebo group. In the pregabalin group, PGIC data were available for 32 patients (97%) and BPI data for 31 patients (94%). Changes in pain diary data and BPI scores are reported as mean changes (95% confidence interval). PGIC is reported as numbers (%).

TABLE 3

Changes in EORTC QLQ-C30 questionnaire scales and items

Variable	Pregabalin (N = 34)	Placebo (N = 30)	Pregabalin vs. placebo	P value
Global health status (quality of life)	9.7 (-0.5-19.9)	-1.7 (-12.4 - 8.9)	11.4 (-3.0 - 25.8)	0.12
Functioning scales				
Physical functioning	0.2 (-7.0 - 7.4)	-2.0 (-8.6 - 4.6)	2.2 (-7.4 - 11.8)	0.65
Role functioning	2.2 (-9.6 - 14.0)	1.7 (-9.7 - 13.1)	0.5 (-15.6 - 16.6)	0.95
Emotional functioning	6.7 (-2.8 - 16.1)	5.4 (-3.7 - 14.4)	1.3 (-11.5 - 14.1)	0.84
Cognitive functioning	4.8 (-4.4 - 14.1)	5.2 (-5.0 - 15.4)	-0.3 (-13.8 - 13.1)	0.96
Social functioning	11.5 (-2.3 - 25.3)	16.1 (4.3 - 27.8)	4.6 (-22.3 - 13.2)	0.61
Symptom scales / items				
Fatigue	-12.2 (-23.8 - -0.6)	2.4 (-9.5 - 14.3)	-14.6 (-30.9 - 1.7)	0.08
Nausea and vomiting	-7.0 (-15.6 - 1.6)	0.0 (-11.0 - 11.0)	-7.0 (-20.5 - 6.6)	0.31
Pain	-17.2 (-30.3 - -4.1)	-4.0 (-16.7 - 8.6)	-13.2 (-31.0 - 4.7)	0.14
Dyspnea	-2.2 (-9.8 - 5.5)	-4.6 (-13.4 - 4.2)	2.4 (-8.9 - 13.8)	0.67
Insomnia	-18.3 (-33.4 - -3.2)	-13.8 (-30.6 - 3.0)	-4.5 (-26.5 - 17.5)	0.69
Appetite loss	-18.9 (-34.0 - -3.7)	-18.4 (-33.8 - -3.0)	-0.5 (-21.7 - 20.7)	0.96
Constipation	-1.1 (-16.0 - 13.9)	4.6 (-6.5 - 15.7)	-5.7 (-24.1 - 12.8)	0.54
Diarrhea	-7.5 (-14.4 - 0.7)	0.0 (-10.7 - 10.7)	-7.5 (-19.8 - 4.7)	0.22
Financial difficulties	-12.9 (-23.7 - -2.1)	-13.8 (-27.6 - 0.0)	0.9 (-16.1 - 17.9)	0.92

QLQ-C30 data were available for 31 patients (94%) in the pregabalin group and for 29 patients in the placebo group (97%). Changes in subscales or items are reported as mean changes (95% confidence interval).

An average reduction in as needed opioid analgesics of 30 mg was observed in the pregabalin group compared to a reduction of 4 mg in the placebo group (P = 0.02). The average body mass index increased 0.5 kg/m^2 in the pregabalin group and decreased 0.2 kg/m^2 in the placebo group (P < 0.001).

Adverse events

During the study period, four patients (12%) in the pregabalin group and two patients (7%) in the placebo group had a serious adverse event (P = 0.7). Two patients in the placebo group and one patient from the pregabalin group were admitted to the hospital due to worsening of abdominal pain. They were treated with additional opioids as rescue medication to reduce pain. One patient receiving pregabalin had pneumonia during the downward taper medication period after study end, one patient receiving pregabalin injured his shoulder in the swing door at the hospital (screening visit; i.e. no study drug administered), and one patient receiving pregabalin experienced worsening of eczema during the trial.

In the pregabalin group 35% of patients reported a feeling of being drunk compared to 7% in the placebo group (P = 0.007). Light-headedness was reported by 24% in the pregabalin group compared to 3% in the placebo group (P = 0.03). Taken together, these significant central nervous system related side effects were present in 29% of patients not taking opioids compared with 52% of patients using opioid analgesics (P = 0.4). Patients with central nervous system related side effects used on average 146 ± 124 mg of morphine per day compared to 92 ± 139 mg in the group not experiencing central nervous system related side effects (P = 0.23). All other adverse events were comparable between groups. Two patients from the pregabalin group stopped the study medication before the end of the study period due to adverse events (confusion and dizziness), and no other patients withdrew the study. Detailed information on adverse events is given in Table 4.

Compliance

In the placebo group, 97% ± 5% of all study medication were taken correctly compared with 91% ± 17% in the pregabalin group (P = 0.4). The number for the pregabalin group envelopes two patients with poor compliance (< 50%), of whom one was withdrawn from the study due to side effects (see Adverse events).

TABLE 4

Adverse events during the study period

	Event	N (%)		Risk ratio (95% CI)	P-value
		Pregabalin (N = 34)	Placebo (N = 30)		
Central nervous system	Any adverse event	31 (91)	16 (53)	1.7 (1.2-2.4)	0.001
	Feeling drunk	12 (35)	2 (7)	5.3 (1.3-21.8)	0.007
	mild/moderate/severe	4 / 7 / 1	0 / 2 / 0		
	Light-headedness	8 (24)	1 (3)	7.1 (0.9-53.2)	0.03
	mild/moderate/severe	6 / 2 / 0	1 / 0 / 0		
	Dizziness	13 (38)	5 (17)	2.3 (0.9 - 5.7)	0.09
	Drowsiness	12 (35)	6 (20)	1.8 (0.8-4.1)	0.27
	Trouble concentrating	3 (9)	1 (3)	2.6 (0.3-24.1)	0.62
	Headache	4 (12)	4 (13)	0.9 (0.2-3.2)	1.00
	Amnesia	2 (6)	0 (0)	-	0.49
	Migraine attack	1 (3)	0 (0)	-	1.00
	Myoclonus	2 (6)	0 (0)	-	0.49
	Tremor	1 (3)	0 (0)	-	1.00
	Dry mouth	4 (12)	0 (0)	-	0.12
Gastrointestinal/ metabolic	Worsening of abdominal pain	3 (9)	4 (13)	0.7 (0.2-2.7)	0.70
	Nausea and vomiting	3 (9)	6 (20)	0.44 (0.1-1.6)	0.28
	Decreased glucose tolerance	1 (3)	0 (0)	-	1.00
	Muscle cramp	0 (0)	1 (3)	-	0.47
	Back pain	1 (3)	1 (3)	0.9 (0.1-13.5)	1.00
Musculoskeletal	Injured shoulder	1 (3)	0 (0)	-	1.00
	Urine retention	1 (3)	0 (0)	-	1.00
Other	Change in sexual function	2 (6)	0 (0)	-	0.49
	Blurred vision	2 (6)	0 (0)	-	0.49
	Pneumonia	1 (3)	0 (0)	-	1.00
	Worsening of eczema	1 (3)	0 (0)	-	1.00

DISCUSSION

Our study demonstrates the efficacy and tolerability of pregabalin as an adjuvant analgesic for the treatment of pain caused by chronic pancreatitis. A dosage of pregabalin between 150 mg and 300 mg twice daily resulted in clinically significant reductions in pain. Entries in daily pain diaries indicated that differences between pregabalin therapy and placebo were apparent three weeks after the first medication administration. The majority of adverse events that were reported by patients taking pregabalin, including feeling of being drunk and light-headedness, were mild to moderate in severity.

As far as we are aware, there are no published studies to date describing the use of pregabalin for pain in patients with chronic pancreatitis. A pain reduction of 36% was seen in the pregabalin group after three weeks of study treatment. Several studies have examined the clinical importance of changes in chronic pain as assessed by a VAS score, and reductions in chronic pain intensity of more than 30% appear to reflect at least

moderately important clinically relevant differences.[15,20] The clinical importance of the observed pain reduction was further supported by the association to self-reported health status (PGIC).[15] Comparable findings have been reported from randomized controlled trials in diabetic polyneuropathy, postherpetic neuralgia, and central neuropathic pain, where maximal analgesic effects were seen after two weeks of treatment.[8,11-13] Also, these findings are in agreement with a recently published meta-analysis where the efficacy and side effects of pregabalin were determined for various neuropathic pain disorders.[9]

The extensive placebo response (24%) seen in the present study was unexpected. In most pregabalin trials, a placebo response of less than 10% has been reported.[8,11-13] A large pain reduction in the group receiving placebo treated may mask the genuine efficacy of pregabalin.[9] It is most likely that this phenomenon explains the discrepancy between the expected effect of 25% pain reduction between groups and the retrieved effect of 12%.

Central nervous system adverse effects were experienced by a number of patients in the pregabalin group, with an incidence comparable to previous studies of gabapentinoids.[9] The adverse effects were mild to moderate in severity and, as seen in the clinic and in previous reports, declined to a tolerable level during the trial course for most patients.[9] This was illustrated by the fact that only two patients had to stop pregabalin treatment before the end of the study period. Furthermore, two-thirds of patients in the pregabalin group rated their global health score as improved after pregabalin treatment, thus emphasizing beneficial analgesic effects over adverse effects for most patients. Patients should, however, be informed of potential central nervous system side effects before the start of pregabalin treatment, including a feeling of being drunk and light-headed, dizziness, and drowsiness.

The majority of patients in the current study were treated with opioids, and one-fourth of patients (N = 19) had undergone interventional therapies for chronic pancreatitis pain. Despite these aggressive treatment approaches, patients still had severe pain at enrollment. Hence, the study population was at the lower end of the treatment algorithm suggested by the American Gastroenterological Association guidelines and thus comprised a patient group that is very difficult to treat.[1] In light of this, the observed treatment response are considered clinical relevant.

The rationale for the present study was based on the hypothesis that the alterations in peripheral and central pain processing underlying pain in patients with chronic pancreatitis resemble those accompanying neuropathic pain. Thus, enhanced neural density and hypertrophy of pancreatic nerves along with up-regulation of pronociceptive mediators in the pancreatic gland were previously reported in patients with chronic pancreatitis.[4,21] In addition, widespread or generalized hyperalgesia has been shown

in chronic pancreatitis pain, along with cortical reorganization and impairments of descending inhibitory control mechanisms, suggesting the presence of aggressive central sensitization in these patients.[5,7,22,23] Taken together, these alterations are similar to those accompanying neuropathic pain and respond poorly to traditional opioid-based approaches.[24,25] On the contrary, gabapentinoids, such as pregabalin, have been shown to be successful in treating pain associated with such nerve damage and hyperalgesia.[9,26] As suggested by the current guidelines from the Initiative on Methods, Measurement, and Pain Assessment in Clinical trials (IMPACCT recommendations), we used several outcome measures to assess the efficacy of pregabalin.[20,27] By using a multidimensional test battery the complex nature of pain can be explored and associations between quantifiable outcomes (such as changes in pain diary scores) can be associated with changes in qualitative outcomes (such as PGIC), and thereby a comprehensive multidimensional impression of the clinical importance of the analgesic efficacy may be obtained. We closely monitored patients using telephone interviews every third day throughout the study period to accurately document side effects and permit dose adjustment in case unacceptable adverse effects were experienced. This approach may explain the good trial adherence, with only two patients leaving the study before the end of the trial period due to side effects.

There are important limitations to this study. First, the follow-up period of three weeks is likely too short to detect changes in functional scales and quality of life. Whether an effect would have been detected on these parameters if the study period was prolonged is unknown, although studies with longer observation periods have reported an improved quality of life in patients with neuropathic pain treated with pregabalin.[8,11,13] Second, the fact that only half of patients had alcohol abuse as cause of chronic pancreatitis may compromise the external validity of the study. In northern Europe, two-thirds of patients with chronic pancreatitis have alcohol abuse as the leading cause of chronic pancreatitis.[28] Third, it would have been of great interest to compare the effects of pregabalin between patients with and without previous pancreatic surgery. However, only one-fifth of patients (N = 11) had previous surgery for pain. Therefore, the study is unlikely to be powered for a sub analysis with stratification on previous surgery. Fourth, the PDQ questionnaire was originally developed and validated in somatic pain (patients with lower back pain) and has never been validated for assessment of visceral pain.[19] Consequently, it may be questioned whether the PDQ is valid for documentation of neuropathic pain in patients with chronic pancreatitis and future studies are awaited to answer this question. For these reasons, the number of patients with neuropathy documented by the PDQ at baseline should be interpreted with caution. Finally, this study does not assess whether pregabalin is suitable for use as a first-line analgesic for treatment of pain in chronic pancreatitis. This important clinical question should be

explored in a future head-to-head study comparing pregabalin with standard analgesics such as opioids and/or interventional treatments. Further studies will also be necessary to document whether pregabalin improves quality of life for patients with chronic pancreatitis pain.

Our study provides evidence that the adjuvant administration of pregabalin for the treatment of pain in patients with chronic pancreatitis is superior to placebo. The side effects reported in the pregabalin group were moderate and in general well tolerated. In conclusion, pregabalin can be used in combination with other analgesics or interventional therapies to obtain better control of the disabling pain in chronic pancreatitis.

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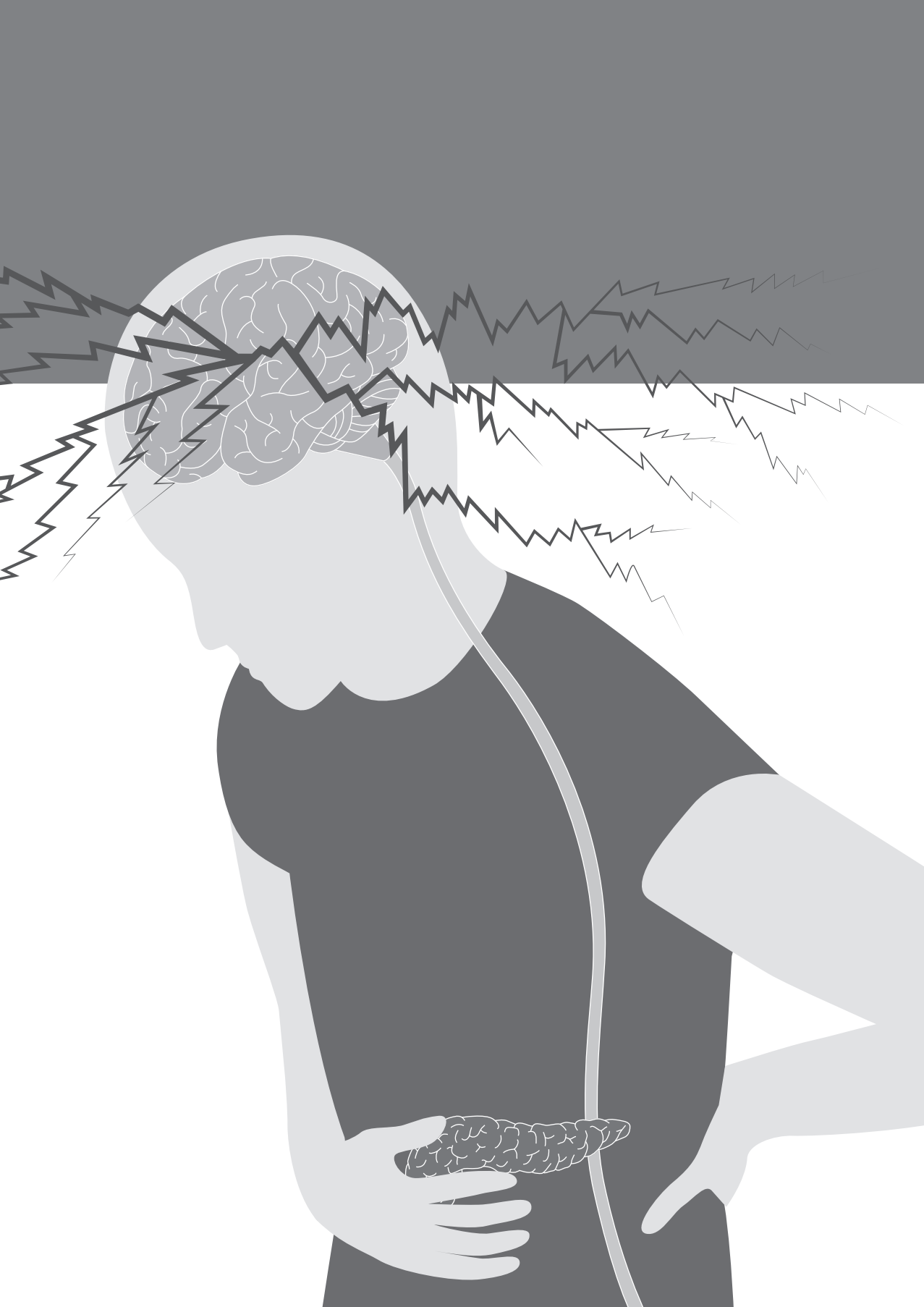

Chapter 8

Effects of pregabalin on central sensitization in patients with chronic pancreatitis in a randomized, controlled trial

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ABSTRACT

Background

Intense abdominal pain is the dominant feature of chronic pancreatitis. During the disease changes in central pain processing, e.g. central sensitization manifest as spreading hyperalgesia, can result from ongoing nociceptive input. The aim of the present study is to evaluate the effect of pregabalin on pain processing in chronic pancreatitis as assessed by quantitative sensory testing (QST).

Methods

This randomized, double-blind, placebo-controlled trial evaluated effects of pregabalin on pain processing. QST was used to quantify pain processing by measuring thresholds to painful electrical and pressure stimulation in six body dermatomes. Descending endogenous pain modulation was quantified using the conditioned pain modulation paradigm to elicit a DNIC (diffuse noxious inhibitory controls) response. The main effect parameter was the change in the sum of all body pain threshold values after three weeks of study treatment versus baseline values between both treatment groups.

Results

Sixty-four patients were analyzed. No differences in change in sum of pain thresholds were present for pregabalin versus placebo after three weeks of treatment. For individual dermatomes, change versus baseline pain thresholds was significantly greater in pregabalin versus placebo patients for electric pain detection threshold in C5 ($P = 0.005$), electric pain tolerance threshold in C5 ($P = 0.04$) and L1 ($P = 0.05$), and pressure pain tolerance threshold in T4 ($P = 0.004$). No differences were observed between pregabalin and placebo regarding conditioned pain modulation.

Conclusion

Our study provides first evidence that pregabalin has moderate inhibitory effects on central sensitization manifest as spreading hyperalgesia in chronic pancreatitis patients. These findings suggest that QST can be of clinical use for monitoring pain treatments in the context of chronic pain.

INTRODUCTION

The treatment of chronic pancreatitis patients can be a major clinical challenge.[1] Achieving control of pain, one of the main symptoms in this disease, can be difficult, and is often unsatisfactory for patients and doctors.[2] An evidence based approach to this pain for these patients does not exist, and to date there are no uniformly accepted guidelines for treatment.

One of the main factors contributing to this problem is the lack of evidence regarding the origin of chronic pancreatitis pain.[3] Complications of pancreatic inflammation such as dilated pancreatic duct, ductal stones and enlarged pancreatic head can be treated endoscopically or surgically, but numerous patients continue to suffer from pain despite technically successful interventions.[4,5] Even bilateral splanchnicectomy, interrupting ascending nociceptive pathways, fails in a substantial number of patients.[6] In the last decade research has suggested that ongoing nociceptive input from the pancreas is not the only explanation for the debilitating abdominal pain in chronic pancreatitis. It is increasingly accepted that changes in central pain processing, e.g. central sensitization or a shift towards pronociceptive pain modulation, may result from chronic nociceptive input, manifest as spreading hyperalgesia.[7-9] Ultimately, this process may become entirely independent of nociceptive input and inhibitory pain modulation, leading to an autonomous pain state.[10]

Medication targeting altered central pain processing, e.g. gabapentinoids such as pregabalin, has been used successfully to treat other chronic pain disorders such as postherpetic neuralgia and neuropathic pain of central origin.[11-13] In a recent publication, we demonstrated that pregabalin has a significant clinical analgesic effect in chronic pancreatitis patients.[14] Quantitative sensory testing (QST) is a useful tool to quantify pain processing in chronic pain patients, also in relation to the effectiveness of analgesic interventions.[15,16] Apart from one recent study on S-ketamine for chronic pancreatitis pain and one using gabapentin for visceral pain in irritable bowel syndrome[12,17], we are not aware of any studies having used QST to describe the influence of centrally active medication on pain processing in patients suffering from chronic pain disorders.

The aim of the present study is to evaluate the effect of pregabalin as adjuvant pain treatment on pain processing, measured by somatic QST, in patients with chronic pancreatitis. We hypothesized that the hyperalgesia in chronic pancreatitis patients with pain will undergo reduction under pregabalin treatment, but not under placebo treatment.

METHODS

Study overview

This study was part of an investigator initiated double-blind, placebo-controlled, parallel-group study of increasing doses of pregabalin conducted in the Netherlands (department of Surgery, Radboud university nijmegen medical center) and Denmark (department of Gastroenterology and Hepatology, Aalborg Hospital, Aarhus University Hospital).[14] The study was approved by the responsible Ethical Committees in both countries (CMO region Arnhem-Nijmegen, Nijmegen, the Netherlands and The local Ethics Committee North Region, Aalborg, Denmark) and all patients provided written informed consent. This article presents a secondary and further analysis of the data obtained in a previous trial focusing primarily on experimental (QST) endpoints.[14]

Patients

For trial inclusion, patients needed to have chronic abdominal pain typical for pancreatitis (i.e. dull epigastric pain more than three days per week for at least three months) and a diagnosis of chronic pancreatitis based on the Mayo Clinic diagnostic criteria.[18] Another inclusion criterion was the use of a stable regime of concomitant analgesic medication during the trial. Exclusion criteria were: painful conditions other than chronic pancreatitis, an abnormal electrocardiogram at screening visit, severe renal impairment, active (or history of) major depression, hypersensitivity to pregabalin or any of it components and pregnant or lactating patients. All patients that participated in this trial were included in this study and analyzed in an intention-to-treat analysis.
Clinical endpoints i.e. pain scores and side effects of the main study are presented in more detail in the original manuscript.[14]

Healthy controls

A control group was recruited in Denmark for comparison with our chronic pancreatitis group to confirm the presence of spreading hyperalgesia at the baseline pre-medication measurement in the pancreatitis group. The controls were completely healthy and had no history of a medical condition that could interfere with our pain measurements.

Randomization and treatment

Eligible patients at our outpatient departments were randomly assigned in a one to one ratio to receive either pregabalin or placebo. A pseudo-random code was computer generated for the randomization blocks that had a size of six. Stratification of trial participants was based on the absence or presence of diabetes mellitus to minimize unbalance in distribution of undiagnosed diabetic polyneuropathy. Patients received increasing doses of either pregabalin or matching placebo for the study period of three weeks. Initial dose was

75 mg pregabalin twice daily. After three days this was increased to 150 mg pregabalin twice daily, with a further increase to 300 mg twice daily after one week and for the rest of the study period. An equivalent regime was followed in the placebo arm. The same oral dosing schedule was prescribed to all patients. Daily dosages were split into two equivalent doses, one administered in the morning between 7.00 a.m. and 10.00 a.m. and one in the evening between 7.00 p.m. and 10.00 p.m. In the case of unacceptable side effects experienced by patients, a single downward dose titration was allowed. Patients had to stay on that final dosage for the remaining study period. Patients were instructed to taper their study medication after three weeks of treatment, by halving their dose for seven days, and then to stop medication. Patients and those administrating study medication, assessing outcomes, and analyzing data were blinded to group assignment.

Study visits

Patients considered for participation in this trial were screened for eligibility and physical fitness. A systematic physical examination including a neurological examination was performed to assess for any relevant conditions and neurological disorders. If eligible, they were randomized by their treating physician for placebo or pregabalin on their second visit, one week after their screening visit. During their second visit all patients had a baseline QST measurement, followed by another QST measurement at the end of the study period of three weeks, i.e. before they were instructed to taper their medication. During the whole study period patients were instructed not to change their daily pain medication. They were only allowed to take extra pain medication in the case of a painful exacerbation of their chronic pancreatitis.

Quantitative sensory testing

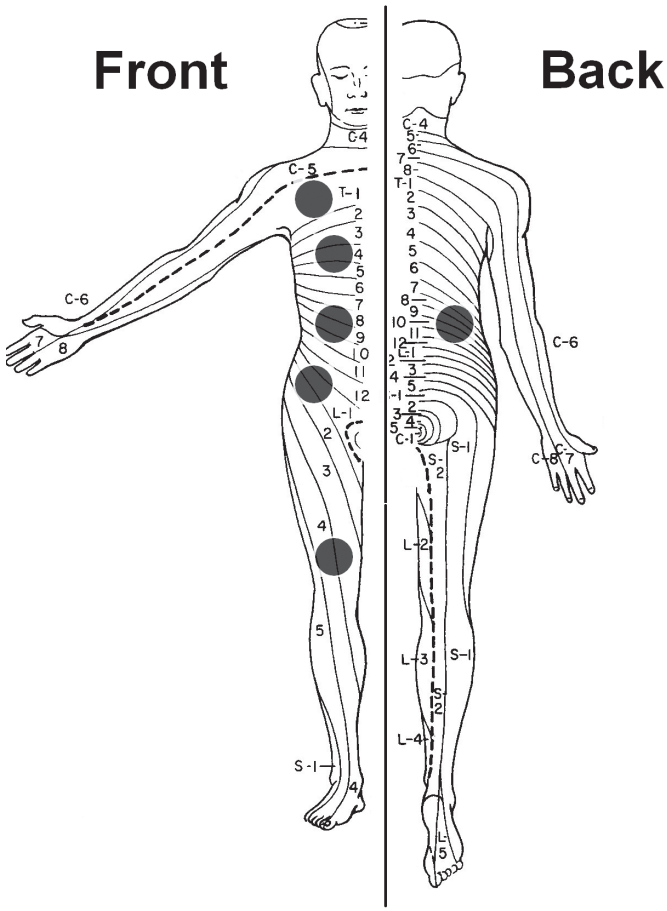
QST took place using a standard temporal test sequence.[7] Testing in females was not standardized with regard to phase of the menstrual cycle because all female pancreatitis patients were amenorrhoeic. Both the examiners (one in Denmark and one in the Netherlands) were trained in and used the same QST protocol. They performed the measurements in the same way and setting. Pressure pain thresholds were based on two measurements and electrical pain thresholds were based on three measurements.

After initial QST training per participating subject, pressure pain thresholds were obtained for muscles overlying bone using a pressure algometer with a 1.0 cm^2 probe (Somedic Sales AB, Horby, Sweden), at each of the following sites on the dominant body side: clavicle (C5 dermatome), sternum (T4 dermatome), pancreatic site (dorsal (BACK) and ventral T10 dermatome), hip region (L1 dermatome) and knee (L4 dermatome) (Figure 1). The pancreas and more distant dermatomes were chosen to observe segmental and spreading hyperalgesia respectively. Two thresholds were measured: pressure pain

detection threshold (pPDT) and pressure pain tolerance threshold (pPTT). As the primary endpoint, the sum of all the thresholds across dermatomes was calculated.[17]

FIGURE 1

Dermatomes of measurement for quantitative sensory testing



Quantitative sensory testing was performed on the following sites on the dominant body side (black dots): clavicle (C5 dermatome), sternum (T4 dermatome), pancreatic site (T10 dorsal (BACK) and ventral dermatome), hip region (L1 dermatome) and knee (L4 dermatome).

Thresholds to electric constant current skin stimulation (Digistim; Biometer A/S, Copenhagen, Denmark; tetanic stimulation at 100 Hz, 0.2 ms square waves, self-adhesive electrodes 3 cm apart) were measured on the dominant side of the body at the

same sites as for pressure pain thresholds. Two thresholds were measured: electric pain detection threshold (ePDT) and electric pain tolerance threshold (ePTT). As the primary endpoint, the sum of all the thresholds was again calculated.[17]

The conditioned pain modulation (CPM, previously known as diffuse noxious inhibitory control (DNIC)) paradigm was performed to test the ability of the patient to generate descending inhibitory modulation.[19,20] Thus pressure pain thresholds (pPTT, the test stimulus) were determined before and after the cold pressor task (the conditioning stimulus), and the CPM effect was determined as the relative change (%) in pressure pain thresholds. For the cold pressor task the dominant hand was immersed in ice-chilled water (1.0 °C ± 0.3 °C) continuously stirred by a pump. The patient was told to remove the hand from the water after two minutes of immersion – or sooner if the pain was considered to be intolerable – and the immersion time noted. Immediately after the cold pressor task, the subjects rated the pain experienced during the test by use of a visual analogue scale for quality control purposes. Pressure pain thresholds were obtained in the non-dominant L4 dermatome (knee) immediately before and after ice water immersion.

Outcome measures

The primary effect parameter for the study was the between group difference (change) in sum of electric or pressure pain thresholds after three weeks of study medication versus baseline values.[17] Between group differences in change in individual dermatome thresholds and CPM paradigm results were secondary endpoints.

Statistical analysis

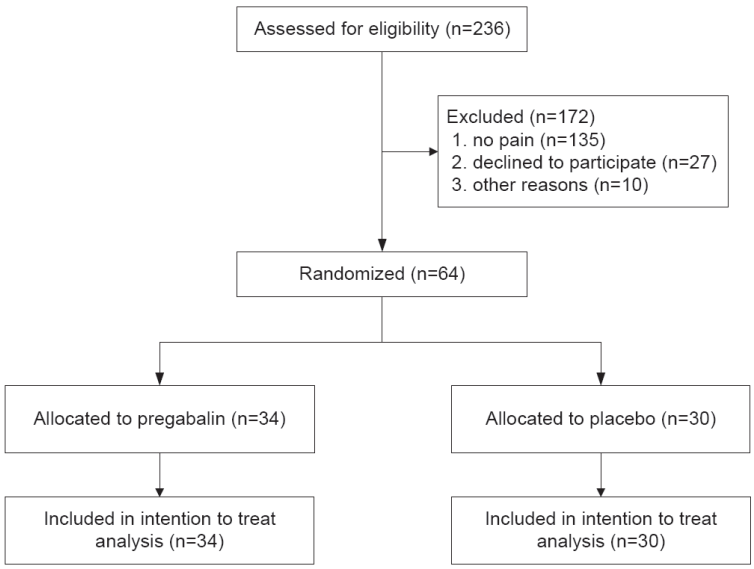
A pre hoc power calculation based on QST as an endpoint was not performed because the study was a part of a randomized clinical trial that investigated pregabalin, powered for a clinical primary endpoint; i.e. change in clinical pain score.

For this mechanistic study we performed an intention-to-treat analysis. We performed statistical analysis using the Statistica for Windows Software Package (Release 7.0, Statsoft Inc, Tulsa, OK, USA). All baseline characteristics and measurements are given as medians with interquartile ranges (IQR). In view of the non-Gaussian data distribution purely non-parametric analysis was performed. Statistical significance was set at $P \leq 0.05$. The sum of all dermatomes for electric and pressure pain detection and tolerance thresholds and the conditioned pain modulation results were compared between the control and the study group using Mann-Whitney U testing to confirm spreading hyperalgesia and pronociceptive pain modulation shift in the pancreatitis patients.[14,17]

We calculated differences (change) in sum of thresholds or individual thresholds between values at pre-medication baseline and after three weeks' medication. We then compared

these differences between the groups using Mann-Whitney U testing. Further analysis consisted of comparison of placebo versus pregabalin groups at pre-medication baseline and after three weeks' treatment for the sum of thresholds, for individual thresholds, or for conditioned pain modulation values using Mann-Whitney U testing.

FIGURE 2
Study enrollment and randomization



The majority of patients not meeting inclusion criteria had passed away, were free of pain or were no longer being treated in either of the hospitals.

RESULTS

Enrollment and baseline characteristics

From October 2008 to May 2010 a total of 236 patients diagnosed with chronic pancreatitis in the last five years in one of both hospitals were screened and 64 patients were randomized; the study was completed without any incident. The majority of patients not meeting inclusion criteria were free of pain, had passed away or were no longer being treated in either of the hospitals. 64 patients completed the study and were finally analyzed in the intention-to-treat analysis (Figure 2). The number of patients randomized to pregabalin or placebo treatment was equally distributed between both hospitals. All patients (24 women, 40 men; median age 53 years (IQR 45 – 62) had pain

due to chronic pancreatitis and were on a stable analgesic therapy. Their median opioid consumption was 60 mg (IQR 11 – 150) of morphine equivalents per day. Their median VAS score before start of trial medication was 4 (IQR 2 – 5) at rest and 5 (IQR 4 – 7) during activity. Demographic data of the placebo and pregabalin group are provided in Table 1. The healthy control group consisted of fifteen volunteers (7 women, 8 men; median age 38 years (IQR 35 – 49). Only age was significantly different between the healthy controls and chronic pancreatitis patients (P = 0.0001).

TABLE 1

Demographic and clinical characteristics of patients

	Pregabalin (N = 34)	Placebo (N = 30)
Age (years)	52 (46 – 58)	55 (42 – 65)
Males - no. (%)	20 (59)	19 (63)
Etiology - no. (%)		
Toxic-metabolic	16 (47)	17 (57)
Idiopathic	11 (32)	11 (37)
Genetic	2 (6)	0 (0)
Autoimmune	1 (3)	0 (0)
Recurrent and severe acute pancreatitis	2 (6)	1 (3)
Obstructive	2 (6)	1 (3)
Diary pain score (visual analogue scale 0 - 10)		
Average pain	4 (2 – 6)	3 (2 – 5)
Maximal pain	6 (4 – 8)	5 (4 – 7)
Concomitant analgesics - no. (%)†		
None	3 (9)	2 (7)
Weak analgesics	7 (21)	11 (37)
Strong analgesics	24 (71)	17 (57)
Morphine equivalents per day (mg)	80 (10 – 158)	49 (13 – 128)
Duration of chronic pancreatitis (months)	92 (55 – 132)	83 (60 – 147)
Diabetes mellitus - no. (%)	10 (29)	10 (33)
Previous interventions for chronic pancreatitis - no. (%)		
Pancreas resection / drainage procedures	6 (18)	5 (17)
Thoracoscopic splanchnic denervation	2 (6)	4 (13)
Patients treated with enzymes for pancreatic exocrine insufficiency - no. (%)	18 (53)	13 (43)
Ongoing alcohol abuse - no. (%)‡	7 (21)	11 (37)
Current smoker - no. (%)	26 (76)	22 (77)

All values are medians with interquartile ranges unless mentioned otherwise. Percentages may not total 100 due to rounding. †Weak analgesics were defined as NSAIDS, paracetamol, codeine and tramadol. Strong analgesics were defined as opioid-based therapies. ‡Alcohol abusing patients were defined as female patients drinking > 14 units of alcohol per week or male patients drinking > 21 units of alcohol per week. 'Pregabalin' is pregabalin study group and 'placebo' is placebo study group. No statistical differences between groups were observed.

Baseline measurements

Pancreatitis versus healthy controls

The sum for pressure and electric pain detection and tolerance thresholds of all dermatomes was significantly lower for the pancreatitis group at baseline versus healthy controls (Table 2). At baseline chronic pancreatitis patients tolerated the cold pressor task for 35 seconds (IQR 24 – 70) and the healthy controls for 180 seconds (IQR 180 – 180), (P = 0.000004). The healthy control group exhibited a significantly greater CPM response than the pancreatitis patients (P = 0.008) (Table 2). These results confirm hyperalgesia and a shift to more pronociceptive pain modulation in our pancreatitis patients.

TABLE 2

Baseline data for conditioned pain modulation and sum of pain thresholds for pancreatitis patients versus healthy controls

	Pancreatitis	Control	P-value
SUM ePDT (mA)	28 (21 – 41)	47 (21 – 65)	0.026
SUM ePTT (mA)	44 (34 – 62)	68 (48 – 92)	0.017
SUM pPDT (kPa)	1912 (951 – 2551)	2285 (2018 – 3018)	0.008
SUM pPTT (kPa)	2694 (2110 – 3185)	3234 (2785 – 4018)	0.005
CPM (%)	4.2 (0.0 – 22.4)	32.6 (10.4 – 41.8)	0.008

All values are medians with interquartile ranges. 'Control' is healthy control group and 'pancreatitis' is chronic pancreatitis group. 'ePDT' is electric pain detection threshold, 'ePTT' is electric pain tolerance threshold, 'pPDT' is pressure pain detection threshold, 'pPPT' is pressure pain tolerance threshold and 'CPM' is conditioned pain modulation.

Pregabalin versus placebo patients

The sum of all dermatomes for pressure and electric pain detection and tolerance thresholds at baseline was similar for the pregabalin versus placebo groups (Table 3). The same applied to the individual dermatomal thresholds (Table 4).

TABLE 3

Sum of pain thresholds for pregabalin versus placebo before and after treatment

	Before		After	
	Pregabalin	Placebo	Pregabalin	Placebo
SUM ePDT (mA)	33.4 (23.6 – 43.5)	23.4 (18.9 – 33.8)	37.3 (27.9 – 51.6) •	26.1 (17.2 – 39.7)
SUM ePTT (mA)	53.4 (39.2 – 67.1)	41.7 (32.6 – 51.6)	52.3 (38.9 – 73.9)	44.0 (34.9 – 55.2)
SUM pPDT (kPa)	1936 (1063 – 2574)	1759 (902 – 2449)	1817 (1109 – 3312)	1817 (844 – 2585)
SUM pPTT (kPa)	2677 (2043 – 3136)	2720 (2307 – 3230)	2798 (2355 – 3945)	2853 (2131 – 3264)

All values are medians with interquartile ranges. 'ePDT' is electric pain detection threshold, 'ePTT' is electric pain tolerance threshold, 'pPDT' is pressure pain detection threshold and 'pPTT' is pressure pain tolerance threshold. • = Measurements after study treatment were significantly higher in the pregabalin group compared to the placebo group.

TABLE 4

Conditioned pain modulation and pain thresholds for pregabalin versus placebo before and after study treatment

	Before		After	
	Pregabalin	Placebo	Pregabalin	Placebo
ePDT (mA)				
C5	3.9 (2.5 - 5.1)	3.5 (2.4 - 6.0)	4.5 (3.4 - 5.6)	3.1 (2.1 - 6.0)
T4	5.0 (3.0 - 7.0)	3.5 (2.7 - 6.3)	6.2 (4.2 - 8.5) •	3.9 (3.3 - 7.6)
T10	5.8 (4.3 - 8.1)	3.7 (3.0 - 7.7)	6.5 (4.7 - 9.2)	4.9 (3.2 - 7.9)
L1	4.8 (3.6 - 6.4)	4.3 (3.1 - 5.9)	6.6 (4.4 - 8.9)	4.7 (2.7 - 8.4)
L4	5.7 (4.0 - 8.5)	4.1 (3.2 - 6.5)	5.8 (4.1 - 9.1) •	4.4 (3.2 - 6.6)
T10 BACK	5.9 (3.8 - 7.2)	4.8 (3.8 - 6.9)	5.8 (4.3 - 10.3) •	4.3 (2.8 - 7.8)
ePTT (mA)				
C5	6.9 (5.4 - 10.7)	5.4 (4.1 - 9.9)	9.6 (5.4 - 14.4) •	6.3 (5.0 - 10.7)
T4	8.9 (5.6 - 13.0)	7.6 (5.1 - 10.7)	10.9 (7.5 - 16.2)	8.6 (5.6 - 11.6)
T10	10.6 (6.1 - 12.7)	7.3 (3.7 - 10.7)	8.8 (6.1 - 15.1)	7.9 (5.6 - 12.6)
L1	9.5 (6.5 - 13.5)	7.2 (5.2 - 11.1)	9.5 (7.0 - 14.8) •	7.1 (5.8 - 12.9)
L4	9.9 (6.7 - 13.3)	7.4 (5.1 - 10.0)	9.1 (6.6 - 14.9)	7.2 (5.7 - 10.9)
T10 BACK	11.7 (6.5 - 16.3)	9.3 (6.4 - 12.6)	9.1 (6.6 - 14.9)	8.9 (6.9 - 12.5)
pPDT (kPa)				
C5	263 (142 - 334)	232 (106 - 380)	228 (130 - 321)	245 (115 - 398)
T4	281 (195 - 392)	289 (139 - 409)	277 (169 - 421)	268 (147 - 359)
T10	166 (97 - 302)	154 (85 - 264)	129 (65 - 328)	157 (61 - 306)
L1	376 (207 - 511)	340 (197 - 571)	292 (207 - 566)	424 (168 - 528)
L4	406 (235 - 601)	396 (176 - 613)	447 (177 - 689)	332 (204 - 641)
T10 BACK	378 (211 - 474)	276 (162 - 522)	332 (132 - 549)	313 (161 - 480)
PTT (kPa)				
C5	421 (313 - 523)	378 (309 - 563)	451 (310 - 614)	459 (358 - 599)
T4	481 (307 - 555)	422 (335 - 528)	431 (352 - 691)	371 (284 - 530)
T10	246 (165 - 493)	257 (176 - 402)	280 (173 - 570)	236 (156 - 432)
L1	578 (454 - 675)	548 (407 - 706)	551 (437 - 716)	581 (479 - 649)
L4	608 (530 - 776)	614 (437 - 776)	733 (526 - 933)	700 (508 - 866)
T10 BACK	574 (403 - 699)	561 (476 - 731)	612 (397 - 838)	537 (395 - 635)
CPM response (%)	0.9 (0.0 - 22.0)	8.9 (0.0 - 23.8)	0.0 (0.0 - 22.4)	0.0 (-4.0 - 19.8)

All values are medians with interquartile ranges. 'ePDT' is electric pain detection threshold, 'ePTT' is electric pain tolerance threshold, 'pPDT' is pressure pain detection threshold, 'pPTT' is pressure pain tolerance threshold and 'CPM' is conditioned pain modulation.• = Measurements after study treatment were significantly higher in the pregabalin group compared to the placebo group.

At baseline, patients in the placebo group tolerated the cold pressor task for 32 seconds (IQR 23 – 98) and in the pregabalin group for 40 seconds (IQR 23 – 60), this was not statistically different between groups. Also no significant difference was found in baseline CPM response between the placebo and pregabalin group (Table 4).

TABLE 5

Change and percentage change in conditioned pain modulation and pain thresholds for pregabalin versus placebo after study treatment

	Pregabalin		Placebo	
	Change	Percentage change (%)	Change	Percentage change (%)
ePDT (mA)				
C5	0.8 (0.2 – 1.9) •	24 (5 – 55)	-0.1 (-0.9 – 0.5)	2 (-25 – 16)
T4	1.5 (-0.7 – 3.0)	39 (-13 – 83)	0.7 (-1.1 – 1.5)	17 (-16 – 49)
T10	0.8 (-0.7 – 3.1)	12 (-11 – 52)	0.4 (-0.7 – 1.4)	8 (-9 – 40)
L1	1.2 (-0.2 – 3.8)	25 (-6 – 71)	0.3 (-0.5 – 2.3)	11 (-11 – 51)
L4	0.9 (-0.8 – 2.3)	14 (-16 – 46)	0.7 (-0.9 – 1.7)	18 (-22 – 37)
T10 BACK	0.6 (-1.2 – 4.3)	16 (-22 – 75)	-0.6 (-1.4 – 1.3)	-14 (-29 – 14)
ePTT (mA)				
C5	2.0 (-0.1 – 3.7) •	25 (-1 – 64)	0.7 (-2.4 – 1.9)	12 (-27 – 40)
T4	2.6 (-0.6 – 5.1)	41 (-5 – 60)	1.5 (-0.9 – 2.9)	15 (-12 – 46)
T10	1.0 (-0.8 – 2.4)	10 (-10 – 27)	0.8 (-1.2 – 2.4)	17 (-9 – 53)
L1	1.9 (-0.8 – 4.9) •	29 (-7 – 59)	-0.2 (-2.3 – 2.1)	-3 (-28 – 38)
L4	1.5 (-2.0 – 5.2)	22 (-20 – 53)	-0.3 (-1.2 – 3.0)	0 (-14 – 83)
T10 BACK	1.1 (-1.9 – 4.8)	10 (-20 – 57)	-0.5 (-2.8 – 2.7)	-5 (-21 – 36)
pPDT (kPa)				
C5	12 (-79 – 89)	7 (-39 – 34)	-13 (-51 – 50)	-7 (-19 – 31)
T4	9 (-91 – 72)	4 (-34 – 26)	-3 (-89 – 45)	-1 (-29 – 13)
T10	13 (-31 – 77)	6 (-31 – 53)	-1 (-51 – 26)	0 (-24 – 15)
L1	63 (-137 – 117)	18 (-39 – 53)	12 (-99 – 135)	9 (-19 – 40)
L4	80 (-129 – 176)	18 (-30 – 37)	0 (-50 – 88)	0 (-13 – 23)
T10 BACK	41 (-63 – 89)	9 (-7 – 31)	34 (-73 – 90)	9 (-24 – 24)
pPTT (kPa)				
C5	19 (-65 – 152)	3 (-17 – 40)	17 (-32 – 103)	5 (-9 – 31)
T4	83 (-24 – 169) •	18 (-7 – 43)	-48 (-108 – 43)	-13 (-21 – 12)
T10	10 (-56 – 111)	5 (-15 – 53)	20 (-103 – 56)	7 (-34 – 23)
L1	-7 (-82 – 136)	-1 (-16 – 32)	69 (-149 – 144)	16 (-19 – 28)
L4	17 (-253 – 278)	6 (-30 – 53)	75 (15 – 225)	12 (3 – 33)
T10 BACK	41 (-74 – 194)	5 (-15 – 40)	14 (-165 – 81)	3 (-27 – 21)
SUM ePDT	6.0 (-1.2 – 15.0)	19 (-6 – 62)	2.3 (-1.9 – 5.8)	9 (-8 – 19)
SUM ePTT	7.6 (-7.1 – 13.5)	13 (-14 – 25)	2.7 (-7.1 – 10.9)	7 (-15 – 28)
SUM pPDT	311 (-155 – 526)	16 (-9 – 39)	131 (-330 – 329)	11 (-14 – 20)
SUM pPTT	226 (-265 – 593)	10 (-14 – 20)	193 (-192 – 380)	8 (-6 – 17)
CPM response (%)	1 (-4 – 18)	-18 (-100 – 134)	-2 (-23 – 6)	-100 (-136 – 16)

All values are medians with interquartile ranges. 'ePDT' is electric pain detection threshold, 'ePTT' is electric pain tolerance threshold, 'pPDT' is pressure pain detection threshold, 'pPTT' is pressure pain tolerance threshold and 'CPM' is conditioned pain modulation.• = Measurements after study treatment were significantly higher in the pregabalin group compared to the placebo group.

Effects of treatment - change in measurements after three weeks' study medication

Electric pain thresholds

There was no significant difference in differences (change) in sums of electric pain detection and tolerance thresholds between the groups (Table 5).

For individual electric pain detection thresholds, difference (change) in dermatome C5 was significantly higher in the pregabalin group (0.8 vs. -0.1, P = 0.005), with a trend for T10 (P = 0.055) (Table 5).

For individual electric pain tolerance thresholds, threshold differences (change) for dermatome C5 (2.0 vs. 0.7, P = 0.04) and L1 (1.9 vs. -0.2, P = 0.05) were significantly higher in the pregabalin group (Table 5).

Pressure pain thresholds

There was no significant difference in differences (change) in sums of pressure pain detection and tolerance thresholds between the groups (Table 5).

There was no significant difference in differences (change) in individual dermatomal pressure pain detection thresholds between the groups (Table 5).

For individual pressure pain tolerance thresholds, threshold differences (change) for dermatome T4 (83 vs. -48, P = 0.004) were significantly higher in the pregabalin group (Table 5).

CPM response

The difference (change) in cold pressor task latency and CPM response was not significantly different between the study groups (Table 5).

Effects of treatment - absolute values after three weeks' study medication

Electric pain thresholds

After three weeks' study medication, sum of all dermatomes for electric pain detection thresholds was significantly higher in the pregabalin versus placebo group (P = 0.01), but not for electric pain tolerance thresholds (Table 3).

For individual dermatomes, electric pain detection thresholds were significantly higher in the pregabalin group (T4; P = 0.04, L4; P = 0.05 and T10 BACK; P = 0.05) (Table 4). For individual dermatomal electric pain tolerance thresholds, C5 (P = 0.05) and L1 (P = 0.03) were significantly higher in the pregabalin group.

Pressure pain thresholds

Sums of – or individual dermatome – pressure pain detection and tolerance thresholds were similar between groups (Table 3 and 4) after three weeks' study medication.

CPM response

After three weeks of study medication patients in the placebo group tolerated the cold pressor task for 42 seconds (IQR 21 – 116) and in the pregabalin group for 46 seconds (IQR 27 – 77); this was not statistically significant. Also no significant difference could be found between groups for CPM response after study medication (Table 4).

DISCUSSION

Our study is the first to demonstrate that a three week treatment with pregabalin in chronic pancreatitis patients results in a moderate antihyperalgesic effect compatible with a reduction of central sensitization. A shift toward more anti-nociceptive pain modulation appears less likely as mechanism due to the unaltered CPM response. Interestingly, this early treatment effect is 1) visible only in dermatomes distant from the referred pancreatic area; and 2) more pronounced for electric skin thresholds than for pressure muscle thresholds. This implies 1) better effects on distant as compared to segmental central sensitization; and 2) more effective hyperalgesia reduction in skin compared to deeper tissues. These results suggest that measuring pain sensitivity using QST may prove useful in monitoring the effects of pain treatment in chronic pancreatitis and help us to diagnose and manage altered pain processing in chronic pain disorders.

Nociceptive input from the pancreas spreads via ascending pathways to spinal and supraspinal central nervous system structures in chronic pancreatitis.[21,22] Ongoing nociceptive input increases neuronal excitability and synaptic strength, initially at the spinal level, a state characterized by hyperalgesia near the site of injury (segmental hyperalgesia).[3,23] With persisting disease and nociception central sensitization spreads rostrally in the central nervous system.[8] This progression is more marked when descending inhibitory control mechanisms fail or in the presence of descending facilitation, and may in due course result in a widespread hyperalgesic state.[9] Ultimately, these central changes may become independent of peripheral nociceptive input, ending in an autonomous state.[6] Sensitization of the nervous system is not specific for chronic pancreatitis, but is common among other chronic pain disorders.[24-26] Congruently with the described course of events, chronic pancreatitis patients in our study did exhibit widespread hyperalgesia compared to healthy controls.

The treatment of pain in chronic pancreatitis patients is usually based on the World Health Organization pain treatment ladder, which ends with opioid treatment. Opioids can provide effective analgesia in some pancreatitis patients, but may have considerable side effects or even induce hyperalgesia.[27] Recently, pain treatments more directly targeting the central nervous system, e.g. tricyclic antidepressants or gabapentinoids, have been introduced to better control disabling pain and hyperalgesia in chronic pain

syndromes.[28] Particularly the use of gabapentinoids has shown clinical results in chronic pain disorders.[12,29,30] The clinical analgesic effect of pregabalin in chronic pancreatitis patients was recently published by our research group.[14] Two studies in an experimental pain model in healthy volunteers showed a reduction of hyperalgesia and central sensitization after gabapentin treatment.[31,32] Only two studies, one with S-ketamine in chronic pancreatitis and one with pregabalin in irritable bowel syndrome, showed comparable reductions of hyperalgesia in patients treated with medication active in the central nervous system.[12,17] To date a more prolonged reduction of somatic hyperalgesia and thus central sensitization has not been demonstrated in chronic pain patients in relation to pregabalin treatment.

In this study we failed to show a significant difference between groups regarding our primary outcome measure (change in sum of thresholds). The significant result regarding secondary outcome measure (change in individual dermatomal thresholds) suggests a moderate effect on spreading hyperalgesia. Interestingly, antihyperalgesic treatment with pregabalin resulted in a greater increase of electric pain thresholds than of pressure pain thresholds after three weeks treatment. A possible explanation is that pregabalin is initially more effective in reducing skin sensitization, as reflected by electric thresholds, as compared to deep tissue sensitization, as reflected by pressure thresholds.[32,33] If this were true, one might expect greater decreases in deep tissue sensitivity with longer treatment periods in future studies.

In this study no significant improvement in CPM could be found, suggesting that the main effect of pregabalin is to directly target central sensitization reflected by hyperalgesia, rather than the pro/anti-nociceptive balance of endogenous modulation. We did, however, demonstrate that before treatment, pancreatitis patients showed less inhibitory pain modulation than healthy controls in accordance with other studies.[9] However, it should be noted that CPM results exhibited considerable variability and are influenced by multiple factors. More research is clearly needed to define the relations between CPM, disease-related changes in central pain processing, and pain treatment effects.[9,34]

A limitation of this study is the relatively small size of the chronic pancreatitis group. A larger sample of chronic pancreatitis patients would appear necessary to provide more detailed and significant evidence of the relation between pregabalin treatment, changes in pain scores and changes in hyperalgesia. While we did find parallel, separate reductions in pain scores and pain sensitivity in our patient collective, the study was not adequately powered to formally study – or prove – correlations between clinical pain reduction and reduction in hyperalgesia. Definitive proof of such a relationship awaits future larger and longer-lasting trials. It should be noted that most chronic pancreatitis studies are small due to the difficulties in recruiting large groups of uniform chronic pancreatitis patients. Better and larger national and international collaborations are necessary to permit larger

and longer population based trials in chronic pancreatitis.

In this study an intention-to-treat analysis was performed conform the international standard for randomized clinical trials. It can be argued that for the mechanistic endpoints an analysis including only patients fully compliant with the study protocol should be performed (per-protocol analysis). We therefore also performed a per-protocol analysis, but we did not present these data in this manuscript, because there were no major differences compared to the intention-to-treat analysis. We checked variability between the study groups and found that standard deviations were comparable between both the groups at the different times. The presence of diabetes mellitus, alcohol consumption and the wide range of morphine dosages might have influenced our results. Certainly some patients might have shown diabetic polyneuropathy or morphine induced hyperalgesia, which could have biased our results. However during the physical examination of trial participants no peripheral sensory or motor disturbances were detected and all baseline characteristics were equally distributed between both treatment groups. There was a significant difference in age between the healthy controls and the chronic pancreatitis patients. The importance of this difference is difficult to assess. Some studies described an increase of pain thresholds during aging[35], others showed no effect[36] and some showed a decrease in thresholds during aging.[37]

Another limitation of the study is the absence of a long-term follow-up. We only measured effects after a relatively short treatment period of three weeks. At this time, modest reductions in distant skin hyperalgesia were already noticeable and significant, albeit without return to normal values (i.e. as in healthy volunteers). This reduction in hyperalgesia occurred in a patient population with a long history of chronic pancreatitis, generally regarded as being particularly difficult to manage.

In conclusion our study provides first evidence that pregabalin modestly reduces the spreading hyperalgesia as manifestation of central sensitization associated with chronic pancreatitis pain. This effect was evident after three weeks of pregabalin treatment and was most evident for electric skin pain thresholds. However more research is needed to predict the long-term effects and define effective dosage schemes for pregabalin use in different stages of chronic pancreatitis.

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Conflict of interests

The study was investigator initiated and Pfizer donated capsules of pregabalin and placebo. The authors have no conflict of interest regarding this manuscript.

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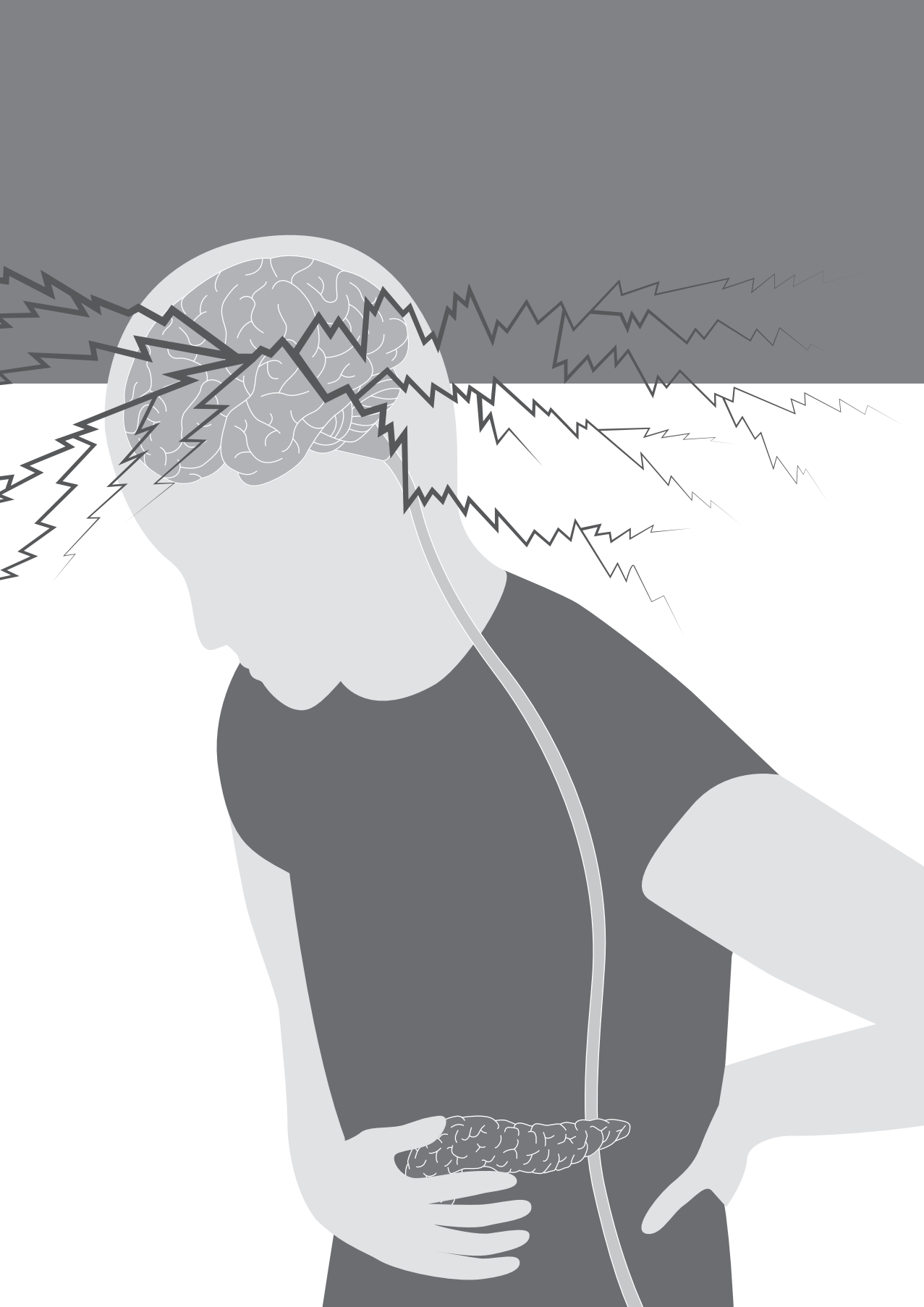

Chapter 9

Pregabalin and placebo responders show different effects on central pain processing in chronic pancreatitis patients

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ABSTRACT

Background

Pain control in chronic pancreatitis is a major challenge; the mechanisms behind analgesic treatment are poorly understood. The study aims to investigate differences in pain sensitivity and modulation in chronic pancreatitis among responders and non-responders to placebo or pregabalin treatment.

Methods

This study was part of a randomized, double-blind, placebo-controlled trial evaluating analgesic effects of pregabalin and placebo in chronic pancreatitis. Post hoc, patients were assigned to one of four groups, i.e. responders and non-responders to pregabalin (N = 16 and N = 15) or placebo (N = 12 and N = 17) treatment. Responders were defined as > 30% pain reduction after three weeks' treatment. We measured change in pain sensitivity before and after treatment, using electric pain detection thresholds (ePDT) in dermatomes C5 (generalized effects) and ventral T10 (segmental effects). Descending endogenous pain modulation was quantified via conditioned pain modulation (CPM) paradigm.

Results

Sixty patients were analyzed in a per-protocol analysis. ePDT change in C5 was significant versus baseline and greater in pregabalin (1.3 mA) versus placebo responders (-0.1 mA, P = 0.015). This was not so for ePDT in ventral T10. CPM increased more in pregabalin (3%) versus placebo responders (-17%, P < 0.001). CPM changed significantly versus baseline only for pregabalin responders (P = 0.006).

Conclusions

Our study provides first evidence that pain relief with pregabalin is associated with antihyperalgesic effects and increased endogenous inhibitory modulation. No such effects were observed in patients experiencing pain relief with placebo treatment. The mechanisms underlying analgesic response to placebo versus drug treatments are different and, together with their interactions, deserve further study.

INTRODUCTION

Morphological changes of the pancreas due to chronic pancreatitis may cause intense pain necessitating surgical or endoscopic intervention. However, many patients remain symptomatic even after surgically successful interventions.[1,2] The majority of these patients have a long history of treatments with opioid-based analgesia with limited effectiveness and undesirable side effects.[3] A good explanation for treatment failure in these patients is lacking to date. Hence, to gain a better control of pain, more evidence is needed on the origin of chronic pain and how this is influenced by pain treatment.

Our study with pregabalin and placebo treatment in chronic pancreatitis showed better pain relief in the pregabalin group compared to placebo treatment. Interestingly a significant pain reduction on average pain could also be observed in the placebo group.[4] Secondary analysis of this trial confirmed that chronic pancreatitis patients showed signs of altered central pain processing which was related to disease stage[5], and inhibitory effects on central sensitization by pregabalin.[6] The impact and the magnitude of placebo analgesia has been described in recent studies and meta-analyses, and is evolving from experimental pain to clinical pain.[7-10] Analysis of the placebo effect has shown that anti-nociceptive placebo effects may be mediated by opioid receptor ligands and that specific brain areas are involved.[11-13] However, more information is needed regarding the mechanisms involved in possible antihyperalgesic and analgesic placebo effects.

Our trial also showed that some patients had a large pain reduction to pregabalin or placebo (responders) and some experienced hardly any pain reduction (non-responders).[14] In animal models, variability in response to pain treatment was related to activity of different pain pathways e.g. the inhibitory GABA(γ-aminobutyric acid)-ergic system or activation of excitatory N-methyl-D-aspartate (NMDA) receptors in the central nervous system.[15-17] Another explanation might be that ongoing nociceptive input by inflammation of the pancreas produces changes in central pain processing which are no longer dependent on ongoing peripheral nociceptive input.[18,19] Exploration of basic pain mechanisms in responder and non-responder groups by quantitative sensory testing (QST) might also help us understand the variable clinical response to pain and placebo treatment between individual patients.

The aim of this study was to investigate the difference in pain sensitivity and modulation by QST in chronic pancreatitis patients who are responders and non-responders to placebo or pregabalin treatment. This study is a secondary analysis of our original randomized controlled trial[4], the population and the design is similar to one of our previous studies.[14]

METHODS

Study oversight

This study was part of an investigator initiated double-blind, placebo-controlled, parallel-group study of increasing doses of pregabalin or placebo conducted in the Netherlands (department of Surgery, Radboud university medical center) and Denmark (department of Gastroenterology and Hepatology, Aalborg University Hospital). The study was approved by the Ethical Committees in both countries (CMO region Arnhem-Nijmegen, Nijmegen, the Netherlands and The local Ethics Committee North Region, Aalborg, Denmark) and all patients provided written informed consent. This article presents a secondary and further analysis of the data obtained in the previous trial focusing primarily on experimental (QST) endpoints.[4]

Patients

Patients needed to have chronic abdominal pain typical for pancreatitis (i.e. dull epigastric pain more than three days per week for at least three months) and a diagnosis of chronic pancreatitis based on the Mayo Clinic diagnostic criteria to be included in this trial.[20] Use of a stable regime of concomitant analgesic medication during the trial was another inclusion criterion. Exclusion criteria were: other painful conditions than chronic pancreatitis, active (or history of) major depression, allergy to pregabalin or any of its components, an abnormal electrocardiogram at screening visit, severe renal impairment, and pregnant or lactating patients. Only the patients completely complying with the described treatment protocol were analyzed in the present per-protocol analysis.
More details regarding clinical endpoints, i.e. pain scores and side effects, is provided in the original manuscript of the main study.[4]

Randomization and treatment

The randomization and study procedures have been described in detail in the original study.[4]
The study consisted of a three week study period of pregabalin or placebo treatment. During the study period patients received either escalating doses of pregabalin (300 to 600 mg/day) or placebo. In the case of unacceptable side effects, a single downward dose titration was allowed. When patients reached their final dosage they had to stay on that regime for the remaining study period. Patients and those administrating study medication, assessing outcomes, and analyzing data were blinded to group assignment. For the whole study period patients were instructed not to change their daily pain medication. Extra pain medication was only allowed in the case of a painful exacerbation of their chronic pancreatitis.

Patients wrote down their average and maximum pain on a visual analogue scale in a pain diary (VAS), where 0 = no pain and 10 = worst pain imaginable.

Study visits

Eligible patients were randomized for placebo or pregabalin on their second visit, one week after their screening visit. After randomization all patients had a baseline QST measurement, followed by another QST measurement at the end of the study period of three weeks, i.e. before they were instructed to taper their medication.

Quantitative sensory testing

QST took place using a standard temporal test sequence. Testing in females was not standardized with regard to phase of the menstrual cycle because all female patients were amenorrhoeic. After initial training, electric pain detection thresholds (ePDT) to electric constant current skin stimulation (Digistim; Biometer A/S, Copenhagen, Denmark; tetanic stimulation at 100 Hz, 0.2 ms square waves, self-adhesive electrodes 3 cm apart) were measured on the dominant side of the body at the following sites: lower neck (C5 dermatome) and pancreatic site (ventral T10 dermatome) (Figure 1). The ventral T10 dermatome was chosen because painful stimuli delivered on this skin area are likely to be processed by the same dorsal horn neurons onto which the nociceptive stimuli coming from the pancreas converge. The C5 dermatome was chosen as a dermatome distant from the pancreas to observe generalized effects on pain thresholds.[18,21]

The conditioned pain modulation (CPM, previously known as diffuse noxious inhibitory controls (DNIC)) paradigm was performed to test the ability of the patient to generate descending inhibitory pain modulation.[22,23] Pressure pain tolerance thresholds (pPTT, the test stimulus) were determined before and after the cold pressor task (the conditioning stimulus), and the CPM effect was determined in the non-dominant L4 dermatome (quadriceps muscle 5 cm proximal to the patella) as the relative change (%) in pPTT. For the cold pressor task the dominant hand was immersed in ice-chilled water (1.0 °C ± 0.3 °C) continuously stirred by a pump. The patient was told to remove the hand from the water after two minutes of immersion - or sooner if the pain was considered to be intolerable – and the immersion time noted. Immediately after the cold pressor task, the subjects rated the pain experienced during the test with a VAS for quality control purposes.[18]

Outcome measures

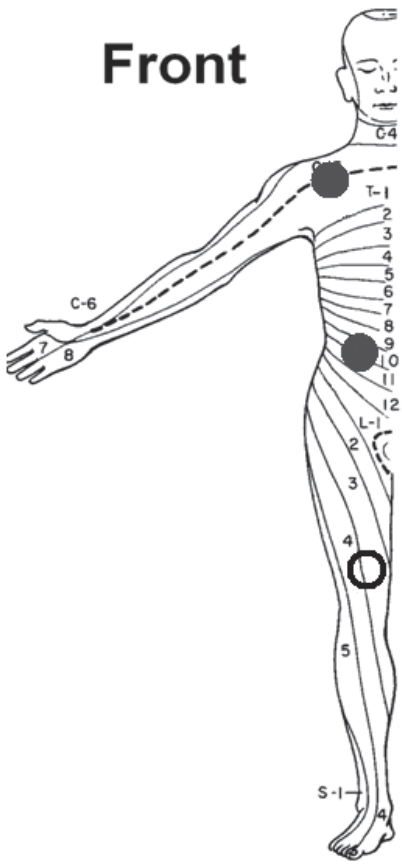
Changes in the following parameters (baseline values vs. after three weeks of study medication) were endpoints of our study:

1. ePDT for dermatomes C5 and ventral T10
2. CPM response

We have chosen ePDT as a QST endpoint for altered pain sensitivity based on publications describing QST measurements before and after pregabalin treatment. These publications showed a strong ePDT response when measurements were compared before and after pregabalin treatment in chronic pancreatitis.[6,14]

FIGURE 1

Dermatomes of measurement for quantitative sensory testing



Quantitative sensory testing was performed on the following sites on the dominant body side (closed dots): lower neck (C5 dermatome) and upper abdominal area (ventral T10 dermatome). Conditioned pain modulation was determined in the non-dominant L4 dermatome (open dot).

Patient groups

Patients in the pregabalin and placebo groups with more than thirty percent pain reduction on their average daily VAS score after three weeks of study medication versus

baseline values were defined as responders. Patients with thirty percent or less pain reduction on their average daily VAS score after three weeks of study were defined as non-responders. The cut-off point was based on clinical pain studies using a numeric rating scale or VAS.[4,14,24,25] Based on study medication and pain reduction, four treatment groups of patients were thus defined: 1) responders placebo group; 2) non-responders placebo group; 3) responders pregabalin group; and 4) non-responders pregabalin group.

Statistical analysis

A pre hoc power calculation based on QST as an endpoint was not performed because the study was a part of a randomized clinical trial that investigated pregabalin, powered for a clinical primary endpoint; i.e. change in clinical pain score. For this mechanistic study we performed a per-protocol analysis.

All baseline characteristics and measurements are given as medians with interquartile ranges (IQR) unless mentioned otherwise.

We performed statistical analysis using the Statistica for Windows Software Package (Release 7.0, Statsoft Inc, Tulsa, OK, USA). Statistical significance was set at $P \leq 0.05$.

Baseline characteristics were compared between groups with Kruskal–Wallis one-way analysis of variance with post hoc analysis using Mann-Whitney U test.

Analysis of incidence of responders and non-responders within the population was by Chi-square Test.

Within the four treatment groups, baseline values and values after three weeks of study medication were analyzed by Wilcoxon signed-rank test for: 1) ePDT in the individual dermatomes and 2) CPM response.

Between the four treatment groups, baseline values and their change after three weeks' treatment were compared using the Kruskal–Wallis one-way analysis of variance with post hoc analysis using Mann-Whitney U for: 1) ePDT in the individual dermatomes; and 2) CPM response. Four subgroups comparisons were performed: 1) placebo responders versus placebo non-responders; 2) placebo responders versus pregabalin responders; 3) placebo non-responders versus pregabalin non-responders; and 4) pregabalin responders versus pregabalin non-responders. Subgroup (post hoc) analysis was conservatively Bonferroni corrected for multiple comparisons (three comparisons, $P \leq 0.016$).

RESULTS

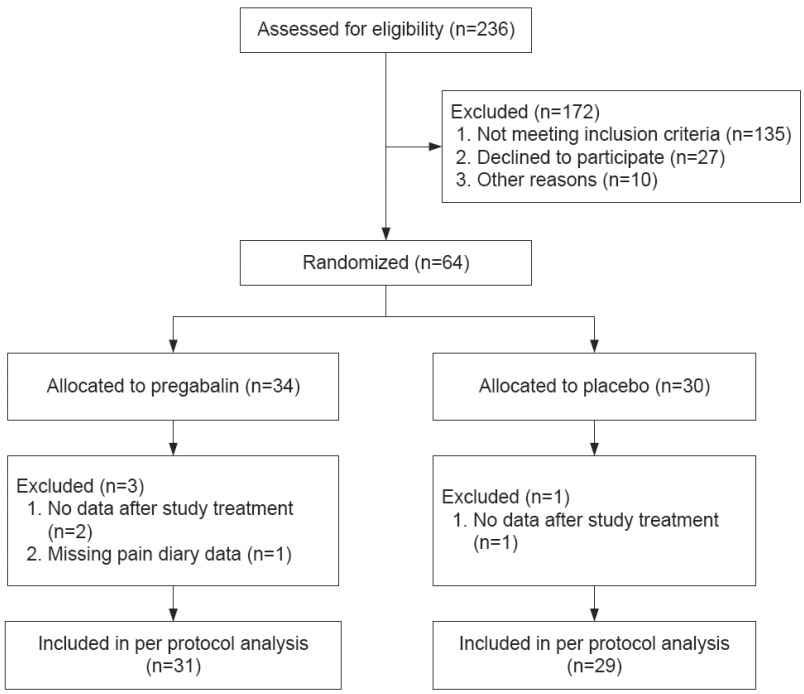
Enrollment and baseline characteristics

From October 2008 to May 2010 a total of 236 patients were screened and 64 patients were randomized. Sixty patients completed the study according to treatment protocol and were finally analyzed (Figure 2). All patients (23 women, 37 men; median age 53

years (IQR 46 – 62)) had pain due to chronic pancreatitis and were on a stable analgesic therapy. Their average daily VAS score before start of trial medication was 4 (IQR 2 – 5) and their maximum daily VAS score was 5 (IQR 4 – 7). Their median opioid consumption was 60 (IQR 9 – 146) mg of morphine equivalents per day. Demographic data of all four patient groups are provided in Table 1 and showed no significant differences, only for VAS after three weeks of study treatment.

FIGURE 2

Study enrollment and randomization



The majority of patients 'not meeting inclusion criteria' had died, were pain free or were no longer being treated in either of the hospitals.

The medians of the average and maximum VAS scores in the pain diaries were comparable at baseline for all (four) treatment groups. Also the pain medication and morphine equivalents per day were comparable at baseline. No significant difference in demographics was found in the incidence of responders and non-responders within the whole group of 60 patients and within the pregabalin and placebo groups (Table 1).

TABLE 1

Demographic and clinical characteristics of patients

	Placebo responders (N = 12)	Placebo non-responders (N = 17)	Pregabalin responders (N = 16)	Pregabalin non-responders (N = 15)
Age (years)	54 (41 – 63)	59 (49 – 64)	52 (50 – 59)	49 (43 – 57)
Males - no. (%)	9 (75)	10 (59)	9 (56)	9 (60)
Etiology - no. (%)				
Toxic-metabolic	9 (75)	7 (41)	6 (38)	9 (60)
Idiopathic	2 (17)	9 (53)	6 (38)	5 (33)
Genetic	0 (0)	0 (0)	1 (6)	1 (7)
Autoimmune	0 (0)	0 (0)	1 (6)	0 (0)
Recurrent and severe acute pancreatitis	0 (0)	1 (6)	1 (6)	0 (0)
Obstructive	1 (8)	0 (0)	1 (6	0 (0)
Diary pain score (VAS before)				
Average pain	4 (2 – 5)	4 (2 – 5)	4 (3 – 5)	4 (2 – 7)
Maximum pain	5 (2 – 7)	5 (4 – 7)	6 (4 – 9)	7 (4 – 8)
Diary pain score (VAS after)*				
Average pain	1 (0 – 2)[#]	4 (2 – 6)	1 (0 – 2)[#]	4 (2 – 6)
Maximum pain	1 (0 – 4)[#]	5 (4 – 7)	2 (1 – 5)[#]	5 (4 – 7)
Concomitant analgesics - no. (%)†				
None	2 (17)	0 (0)	2 (13)	1 (7)
Weak analgesics	3 (25)	8 (47)	4 (25)	3 (20)
Strong analgesics	7 (58)	9 (53)	10 (63)	11 (73)
MEQ/day (mg)	45 (23 – 135)	48 (8 – 120)	71 (4 – 127)	80 (10 – 180)
Duration of chronic pancreatitis (months)	151 (77 – 212)	84 (73 – 112)	83 (54 – 131)	117 (100 -166)
Diabetes mellitus - no. (%)	6 (50)	4 (24)	7 (44)	3 (20)
Previous interventions for chronic pancreatitis – no. (%)				
Pancreas resection / drainage procedures	2 (17)	3 (18)	3 (19)	3 (20)
Thoracoscopic splanchnic denervation	1 (8)	3 (18)	0 (0)	2 (13)
Celiac blockade	1 (8)	0 (0)	1 (6)	0 (0)
Enzyme treatment for pancreatic exocrine insufficiency - no. (%)	6 (50)	6 (35)	7 (44)	8 (53)
Ongoing alcohol abuse - no. (%)‡	4 (33)	6 (35)	3 (19)	3 (20)
Current smoker - no. (%)	9 (75)	13 (76)	12 (80)	12 (75)

All values are medians with interquartile ranges unless mentioned otherwise. Percentages may not total 100 due to rounding. 'VAS' is Visual Analogue Scale (0 – 10). †Weak analgesics were defined as NSAIDS, paracetamol, codeine and tramadol. Strong analgesics were defined as opioid-based therapies. 'MEQ' is morphine equivalents per day, 'pregabalin' is pregabalin study group and 'placebo' is placebo study group. ‡Alcohol abusing patients were defined as female patients drinking 14 units of alcohol per week or male patients drinking 21 units of alcohol per week. [#]A significant reduction in mean and maximum VAS score was observed within the treatment group after study treatment ($P \leq 0.010$). *Statistical differences between groups where the placebo responders and pregabalin responders differed significantly ($P \leq 0.010$) from the placebo non-responders and pregabalin non-responders.

Pain characteristics

Within the treatment groups both responder groups showed a decline in the average and maximum VAS score after treatment (less pain), this was significant for the responder placebo group for average (P = 0.003) and maximum (P = 0.003) VAS score and for the pregabalin responder group for average (P = 0.001) and maximum (P = 0.001) VAS score (Table 1). The median percentage reduction in average VAS score after three weeks of study treatment was 75% (IQR 54 – 100) for the placebo responder group and 69% (IQR 48 – 94) for the pregabalin responder group. Between all treatment groups these results were significantly different compared to the non-responder placebo and pregabalin groups ($P \leq 0.001$) (Table 1).

Electric pain detection thresholds in Individual dermatomes

At baseline ePDT in the C5 and ventral T10 dermatomes were comparable between treatment groups. Within treatment groups, only pregabalin responders showed a significant increase in electric pain detection thresholds (less hyperalgesia following pregabalin treatment) for the C5 dermatome (P = 0.009) and ventral T10 dermatome (P = 0.009) (Table 2).

C5 dermatome (widespread hyperalgesia): Changes in ePDT for the C5 dermatome were significantly different between the four treatment groups overall (H=10.63, P = 0.014). Post hoc analysis showed that the pregabalin responders group differed significantly (less hyperalgesia following pregabalin treatment) from the patients in the placebo responders group (P = 0.015) (Table 2) (Figure 3).

Ventral T10 dermatome (segmental hyperalgesia): No significant differences between groups were seen for changes in ePDT in the ventral T10 dermatome (H = 5.14, P = 0.162) (Table 2) (Figure 4).

Conditioned pain modulation

The CPM response was comparable for all four patient groups at baseline. Within groups the pregabalin responders showed a significant increase in CPM response, i.e. a more effective response, after three weeks of treatment (P = 0.006). In contrast the placebo responders showed a non-significant trend for a decrease in CPM response, which is a less effective response (more pronociceptive pain modulation), after three weeks of treatment (P = 0.028) (Table 2).

The changes in CPM responses were significantly different between groups (H = 11.3, P = 0.01). Post hoc analysis showed that the pregabalin responders had a CPM response, which differed significantly from that of patients in the placebo responders group ($P < 0.001$) (Table 2) (Figure 5).

TABLE 2

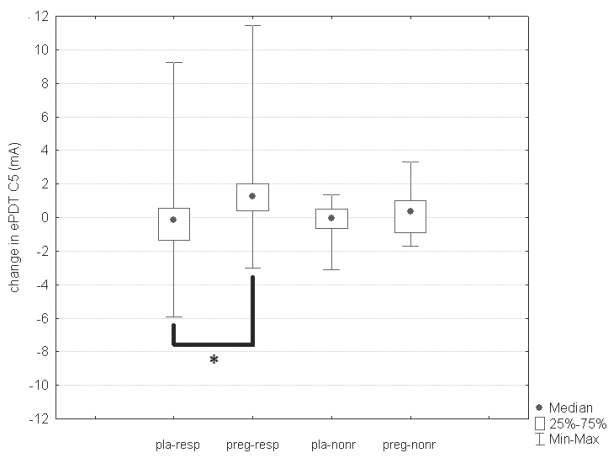
Pain thresholds and conditioned pain modulation response at baseline, after three weeks' treatment and the change in values for all groups

	Placebo responders (N = 12)	Placebo non-responders (N = 17)	Pregabalin responders (N = 16)	Pregabalin non-responders (N = 15)
ePDT (mA) (baseline)				
C5	3.5 (2.4 – 7.6)	3.5 (2.2 – 5.5)	3.8 (2.7 – 4.7)	3.6 (2.2 – 5.1)
T10V	6.1 (3.5 – 7.8)	3.5 (2.5 – 6.8)	5.7 (4.5 – 7.6)	5.2 (4.5 – 10.4)
ePDT (after treatment)				
C5	5.0 (2.0 – 6.3)	2.3 (2.1 – 4.5)	4.8 (3.5 – 6.3)*	4.5 (3.3 – 5.4)
T10V	7.0 (5.0 – 8.2)	3.4 (3.0 – 6.1)	6.8 (5.8 – 10.1)†	6.4 (3.9 – 7.5)
Change ePDT				
C5	-0.1 (-1.3 – 0.5)	-0.3 (-0.7 – 0.6)	1.3 (0.4 – 2.0)	0.4 (-0.9 – 1.3)
T10V	0.7 (-0.6 – 1.9)	-0.2 (0.8 – 1.2)	1.7 (0.0 – 3.4)	-0.3 (-1.1 – 1.9)
CPM response (%) (baseline)	13 (-3 – 25)	14 (5 – 44)	11 (-12 – 23)	12 (-19 – 39)
CPM response (%) (after treatment)	-3 (-12 – 9)	17 (-2 – 36)	15 (0 – 50)‡	0 (-1 – 23)
Change CPM response (%)	-17 (-35 – -6)	3 (-22 – 10)	9 (4 – 55)	-7 (-35 – 16)

All values are medians with interquartile ranges. 'ePDT' is electric pain detection threshold, 'CPM' is conditioned pain modulation. C5 is the C5 dermatome (lower neck) and T10V is the ventral T10 dermatome (upper abdominal area). Statistical difference between baseline and after treatment values: *: P = 0.009, †: P = 0.009 and ‡: P = 0.006.

FIGURE 3

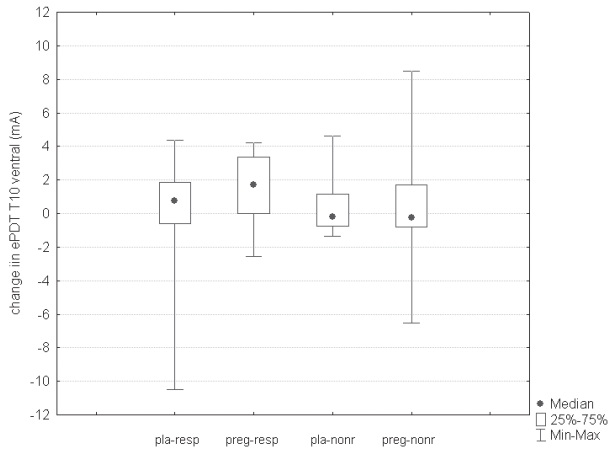
Change in electric pain detection thresholds at dermatome C5



Values are medians with interquartile ranges. 'ePDT' is electric pain detection thresholds. 'pla-resp' is the placebo responders, 'preg-resp' is the pregabalin responders group, 'pla-nonr' is the placebo non-responders group and 'preg-nonr' is the pregabalin non-responders group. Significant differences are marked with an asterisk (P = 0.015).

FIGURE 4

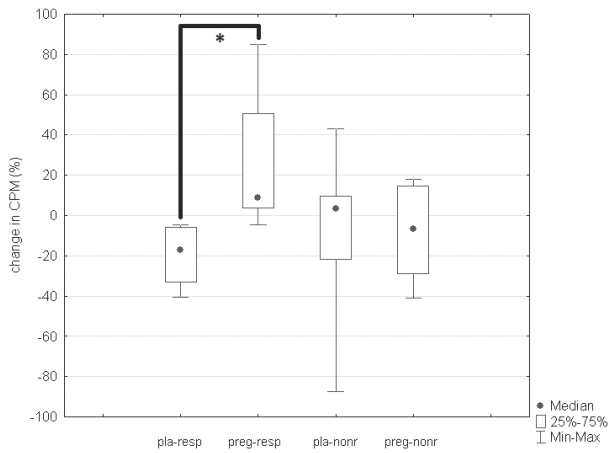
Change in electric pain detection thresholds at dermatome ventral T10



Values are medians with interquartile ranges. 'ePDT' is electric pain detection thresholds. 'pla-resp' is the placebo responders, 'preg-resp' is the pregabalin responders group, 'pla-nonr' is the placebo non-responders group and 'preg-nonr' is the pregabalin non-responders group.

FIGURE 5

Change in conditioned pain modulation response



Values are medians with interquartile ranges. 'CPM' is conditioned pain modulation response. 'pla-resp' is the placebo responders, 'preg-resp' is the pregabalin responders group, 'pla-nonr' is the placebo non-responders group and 'preg-nonr' is the pregabalin non-responders group Significant differences are marked with an asterisk ($P < 0.001$).

DISCUSSION

This is the first study to describe the relation between the clinical analgesic response; defined as responders and non-responders, to placebo or pregabalin treatment and changes in pain processing using QST measures in patients with chronic pancreatitis. Our study shows the presence of significant antihyperalgesic effects (decrease in pain sensitivity) in pregabalin responders and no significant antihyperalgesic effects in placebo responders. Pregabalin responders showed significantly more antihyperalgesic effects compared to pregabalin non-responders. With treatment pregabalin responders' descending pain modulation (CPM response) became significantly more inhibitory – while that of placebo responders showed a trend towards becoming more facilitatory.

Our results indicate that both underlying mechanisms and the placebo effect need to be taken into account in the clinical management of pain in chronic pancreatitis. Firstly, the response to placebo analgesia was not accompanied by significant anti-hyperalgesia. Thus mechanisms other than anti-hyperalgesia appear to operate in placebo analgesia. Secondly, only in the pregabalin responders did pain thresholds within and distant from the pancreatic segment increase significantly. Distant from the pancreatic segment, this antihyperalgesic effect was significantly larger in pregabalin responders versus non-responders. In the pancreatic segment the antihyperalgesic response to pregabalin treatment did not differ significantly between pregabalin responders and non-responders. This suggests that analgesic response to pregabalin treatment is linked to antihyperalgesic effect, although other mechanisms may also be operating. Furthermore, generalized antihyperalgesic effects appear more prominent than segmental antihyperalgesic effects. Thirdly, it would appear that endogenous descending pain modulation plays an important role in analgesic response and may be fundamentally different for placebo versus pregabalin treatments.

Effect of pregabalin

Treatments targeting the central nervous system e.g. gabapentinoids or tricyclic antidepressants are increasingly being demonstrated to improve management of chronic pain disorders.[26] For chronic pancreatitis we have shown pregabalin to be effective in reducing pain scores after three weeks of treatment together with a positive overall treatment response as rated by patients.[4] Accompanying the clinical effect we found an antihyperalgesic effect of pregabalin for electric stimuli.[6] The present study further elucidates these results, by showing that anti-hyperalesic effects in responders to pregabalin are significant particularly in a dermatome distant from the pancreas. The overall size of the effect in the pancreatic segment was comparable between pregabalin responders and non-responders. In another study we showed that chronic pancreatitis patients with segmental hyperalgesia had a superior clinical response to pregabalin.[27]

Taking these two results together, this suggests that the major antihyperalgesic effect of pregabalin is on ascending spinal sensitization rather than directly on sensitization within the pancreatic spinal segment. Clearly further research is needed regarding sites of action of pregabalin within the nervous system. Although baseline CPM values were similar, modulatory responses were greater and significantly inhibitory in pregabalin (vs. placebo) responders. This outcome could be construed as a direct, anti-facilitatory effect of pregabalin on CPM, or an indirect one based on reduction of ascending central nociceptive transmission.[22] If pregabalin affects ascending central pathways, it might also affect descending ones, an explanation which could support direct effects on CPM. A further possible explanation could be other differences between the pregabalin responder and non-responder patients, i.e. regarding the use of more strong analgesics or a history of more pain reducing previous interventions. Responders and non-responders to gabapentin have been described in a rat study where rats with selective nerve injury (spinal level) showed differences in descending inhibition. The extent of suggested changes in the central nervous system may predict the effect of pregabalin and gabapentin treatment.[28]

Effect of placebo

The placebo effect on clinical pain has been described extensively.[29-31] Imaging studies of the brain have shown increased activity in pain-related areas during painful stimuli and placebo analgesia.[32] A relation has been demonstrated between desire for pain relief or expected pain levels and opioid-related activity in certain brain areas. These psychological factors and placebo effect can be antagonized by naloxone.[33] The effect of placebo analgesia appears to be highly variable and depends on contextual factors.[11,34,35] In our clinical study we found a strong placebo response albeit significantly lower than with pregabalin treatment.[4] This placebo response may be explained by the psychosocial context and in the suggestion of treatment effect.[30,31,36] Chronic pancreatitis patients, with their extensive medical history, their expectation or desire for pain relief, and the possibility of being randomized for pregabalin may be particularly susceptible to placebo effects.

Our study showed that the placebo responders had a significant strong clinical effect on clinical pain compared with placebo non-responders. However we also demonstrated no significant antihyperalgesic effects for both responders and non-responders to placebo. Since effects on skin pain sensitivity were similar in placebo responders and non-responders, central anti-hyperalgesia is unlikely to be the mechanism underlying placebo analgesia, at least in chronic pancreatitis patients. Furthermore, a trend to decrease in inhibitory CPM response was seen only in placebo responders. Theoretically, this finding could be linked to a negative interaction of placebo effect with CPM. This unexpected

trend result further suggests that anti-hyperalgesia is not a major mechanism underlying analgesia in this context. Clearly, more research is necessary.

Limitations

A limitation of this study is the relatively small size of the four patient groups. Nevertheless, significant differences could be observed between the groups. Furthermore, we may have introduced bias by using a per-protocol analysis. However we think that analyzing only the patients that fully complied to the study protocol i.e. used all their study medication and had measurements after study treatment is the proper way to investigate mechanisms in responders and non-responders to the trial medication. It should be noted that the majority of patients in both study arms where compliant and all study medication was taken correctly. The duration of study medication in the initial trial was three weeks; perhaps a longer study period would have given a more distinct difference between both groups. In our clinical study 39% of pregabalin patients did not tolerate 300 mg pregabalin twice daily, and were treated with 150 mg twice daily. The distribution of patients not tolerating 300 mg twice daily was not significantly different between the pregabalin responders and non-responders. Perhaps in a larger population this difference could be off significance. Another source of bias could have been that the groups were not comparable at baseline for factors we didn't measure, i.e. expectations regarding study effect or other psychological measures. However this seems unlikely because no significant differences could be found in the clinically relevant baseline characteristics between the four groups. Also no differences in baseline values were found for use of strong analgesics, morphine equivalents per day, prevalence of diabetes mellitus, nicotine exposure or alcohol consumption (possible confounding effects on pain perception) between all four groups.

Summary

Our study provides first evidence that patients treated with placebo show no antihyperalgesic effects paralleling pain relief after a treatment period of three weeks in chronic pancreatitis. Patients with a positive effect on clinical pain following pregabalin treatment were the only ones to show significant antihyperalgesic effects, particularly in the dermatome distant from the pancreas, with comparable antihyperalgesic effects for pregabalin responders and non-responders in the pancreatic dermatome itself. Pregabalin responders showed an increase in endogenous inhibitory modulation compared to a trend to decrease in placebo responders. Both the existence of a potent placebo effect and the difference between responders and non-responders regarding underlying pain sensitivity and modulation need to be taken into account in the management of pain in chronic pancreatitis.

ACKNOWLEDGEMENTS

Conflict of interests

The study was investigator initiated and Pfizer donated capsules of pregabalin and placebo. The authors have no conflict of interest regarding this manuscript.

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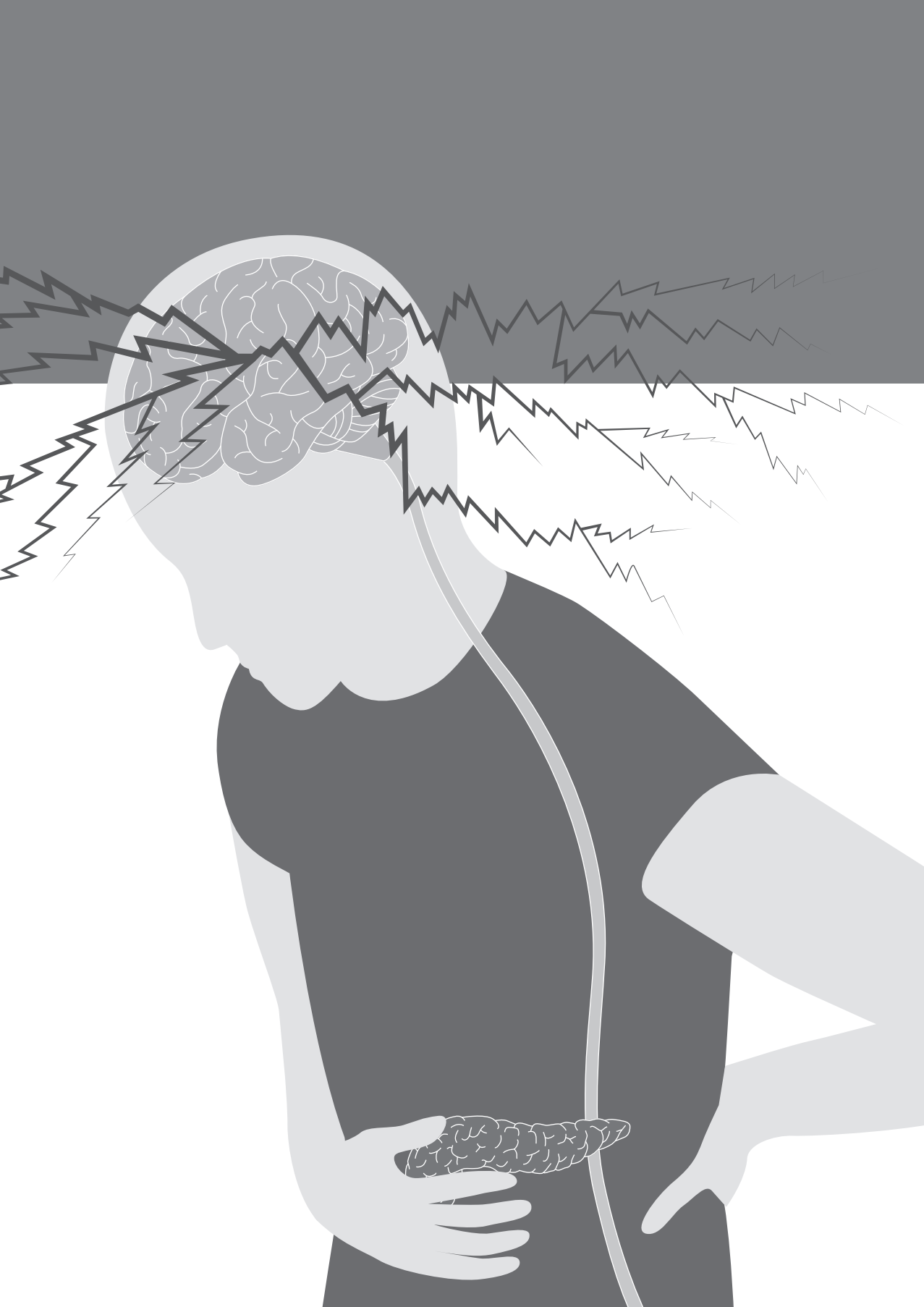

Chapter 10

General discussion and future perspectives

Adapted from:

Systematic mechanism-orientated approach to chronic pancreatitis pain

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ABSTRACT

Pain in chronic pancreatitis shows similarities with other visceral pain syndromes (i.e. inflammatory bowel disease and esophagitis), which should thus be managed in a similar fashion. Typical causes of chronic pancreatitis pain include increased intrapancreatic pressure, pancreatic inflammation and pancreatic/extrapancreatic complications. Unfortunately, chronic pancreatitis pain continues to be a major clinical challenge.

It is recognized that ongoing pain may induce altered central pain processing, e.g. central sensitization or pronociceptive pain modulation. When this is present conventional pain treatment targeting the nociceptive focus, e.g. opioid analgesia or surgical/endoscopic intervention, often fails even if technically successful. If central nervous system pain processing is altered, specific treatment targeting these changes should be instituted (e.g. gabapentinoids, ketamine or tricyclic antidepressants).

Suitable tools are now available to make altered central processing visible, including quantitative sensory testing (QST), electroencephalography (EEG) and (functional) magnetic resonance imaging ((f)MRI). These techniques are potentially clinically useful diagnostic tools to analyze central pain processing and thus define optimum management approaches for pain in chronic pancreatitis and other visceral pain syndromes.

The present review proposes a systematic mechanism-orientated approach to pain management in chronic pancreatitis based on a holistic view of the mechanisms involved. Future research should address the circumstances under which central nervous system pain processing changes in chronic pancreatitis, and how this is influenced by ongoing nociceptive input and therapies. Thus we hope to predict which patients are at risk for developing chronic pain or not responding to therapy, leading to improved treatment of chronic pain in chronic pancreatitis and other visceral pain disorders.

INTRODUCTION

Chronic pancreatitis involves progressive inflammatory changes of the pancreas resulting in morphological alterations and loss of pancreatic endocrine and exocrine function.[1] Quality of life is impaired and life expectancy is reduced.[2,3] The two main clinical manifestations of chronic pancreatitis are pancreatic insufficiency and (chronic) abdominal pain. Pancreatic insufficiency is marked by exocrine dysfunction resulting in impaired food digestion and absorption, and endocrine dysfunction which results in diabetes mellitus.[1] Pain in chronic pancreatitis is considered to be of visceral origin. When compared to other (chronic) visceral pain syndromes there are many similarities with the pain presentation of chronic pancreatitis patients. The pain of chronic pancreatitis is typically present as chronic epigastric pain, often radiating to the back, severe, dull, worse after eating and exhibiting episodic flares. This conforms to typical clinical characteristics of visceral pain which are: 1) the pain is not always simply or directly linked to morphological changes of the diseased organ; 2) pain is diffuse and poorly localized; 3) the pain may be referred to other locations; and 4) the pain is accompanied by motor and autonomic reflexes (vomiting, nausea and muscle tension).[4] These parallels suggest that chronic pancreatitis pain provides a useful model for the diagnosis and treatment of visceral pain syndromes with an identifiable nociceptive source in general.

Pain management in chronic pancreatitis is at present mostly aimed at the nociceptive source, the pancreas. General recommendations include correction of pancreatic insufficiency and management of local complications, flanked by dietary modifications and cessation of alcohol use and smoking.[1] Currently a conservative step-up approach is advocated for pain treatment in chronic pancreatitis, consisting of symptomatic pain relief and dealing with the pancreas as nociceptive source. For symptomatic pain relief, patients are treated with analgesics based on the 'pain relief ladder' provided by the World Health Organization.[5] When such analgesic therapy is not successful, patients usually are referred for endoscopic interventions to attempt to reduce nociceptive input from the diseased pancreas. Eventually, patients may be referred for invasive surgical intervention if pain still persists despite prolonged analgesic (usually opioid) use and multiple endoscopic interventions (up to 75% of all patients).

Usually endoscopic interventions are performed for pancreatic duct strictures (stenting) and pancreatic duct stones (extracorporal shockwave therapy). Multiple surgical procedures have been described in the literature, all with different indications and success rates.[6] Drainage procedures like the pancreaticojejunostomy are performed for an enlarged pancreatic duct. When an enlarged pancreatic duct with an inflammatory mass in the pancreatic head is present, usually a Frey or Beger procedure is performed. Indications for (partial) pancreatic resections, i.e. pancreaticoduodenectomy, distal pancreatectomy and total pancreatectomy, are inflammatory masses in the head or tail

of the pancreas, or failure of other therapies. Alternative approaches for dealing with the pancreas as a nociceptive source include deafferentation techniques such as nerve blocks and denervation procedures like bilateral thoracoscopic splanchnicectomy, which have shown to be beneficial for pain reduction in chronic pancreatitis patients.[7] The success rate in terms of pain reduction after endoscopy or surgery is highly variable.[6] The optimal timing of interventions and which patients should be treated endoscopically or surgically continues to be intensively debated.[6] Despite these many management options, a significant number of chronic pancreatitis patients continue to experience pain even after conventional successful treatments, resulting in recurrent hospitalization, opioid dependence and severely impaired quality of life.[8,9]

It is increasingly accepted that in many patients with refractory chronic pain, the pain may be the result of abnormal central pain processing which should be taken into account and targeted when pain management is planned.[10] This is in line with the key new insight of the last two to three decades of pain research, demonstrating that the central nervous system is not hard-wired, but rather highly plastic in the face of ongoing nociceptive input, exhibited as extensive alterations in central pain processing.[10] These changes typically involve increased pain sensitivity and facilitatory changes in modulation of painful inputs.[11-13] Further support for this view comes from recent successful studies with non-classical analgesic medication, i.e. S-ketamine and pregabalin, which targets mainly the central nervous system, and which has been shown to be effective in both visceral and somatic chronic pain syndromes.[11,14,15]

To optimize (pain) treatment in chronic pancreatitis, it is thus evident that we need to move away from approaches exclusively based on dealing with peripheral nociceptive input from the pancreas towards more holistic strategies taking into account alterations in central pain processing due to ongoing nociceptive inputs. The aim of this review is to highlight the recent progress in understanding the central mechanisms underlying chronic pain in chronic pancreatitis and its impact on pain management. We present the evidence presently available that such central changes take place and operate in the human clinical context. Next, we focus on the diagnostics that are currently available to measure/visualize changes in central pain processing and how these are related to chronic pain in chronic pancreatitis and other chronic abdominal visceral pain syndromes. Finally, based on these diagnostics we propose a new systematic mechanism-orientated approach to diagnosing and treating pain in chronic pancreatitis as an example of an abdominal visceral pain syndrome.

A SYSTEMATIC MECHANISM-ORIENTATED APPROACH TO CHRONIC PAIN

Even after tissue healing, pain may persist as chronic pain with a major impact on quality of life. To date, the majority of publications on chronic pain adopt an empirical approach to the treatment of such pain, primarily based on dealing with the putative peripheral nociceptive source of the pain. At present, a holistic systematic mechanism-orientated approach to the prevention and treatment of chronic pain is lacking.

The key: altered pain processing

A key insight has been that nervous system processing of pain is not hardwired: sensory processing in the central nervous system typically changes as a result of noxious sensory inputs.[16] Acute nociception initially results in increased pain sensitivity (hyperalgesia) affecting the peripheral and central nervous system. When ongoing nociception (due to ongoing damage to tissues and nerves) is present, it initially sensitizes the peripheral nervous system. Subsequently, such ongoing nociceptive barrage will excite the spinal cord, brainstem and brain leading to central sensitization. In the end the whole nervous system may become sensitized, leading to exaggerated pain with minor stimuli (hyperalgesia) or even pain without nociceptive input (allodynia).[16-18] Counteracting modulatory responses to nociceptive input like descending inhibition may fail as well, or even become facilitatory, resulting in more pain.[8]

The four key questions

To achieve a holistic and systematic mechanism-orientated approach to chronic pain four key questions need to be answered.[18]

1) What is the source of nociception? The majority of chronic pain disorders start off with a nociceptive source. Knowledge of the source enables us to aim our therapy at it and provides us with information regarding the type and intensity of nociception (e.g. visceral vs. somatic pain).

2) Is nociceptive transmission altered? A common reason for altered nociceptive transmission by peripheral nerves to the central nervous system is peripheral nerve sensitization and damage. Nerve damage is a strong predictor for pain that is difficult to control or treat and can become a source of nociceptive input in itself. Nerve damage is associated with extensive and aggressive alteration in central nervous system function.[19] In addition, cytokines, hormones and other acute phase proteins may be released due to pathological processes and may facilitate sensitization of the central nervous system, e.g. via humoral pathways.[8,20]

3) Is central pain processing altered? The first alteration in central nervous system processing to be taken into account is central sensitization, defined as an increased responsiveness of central pain transmitting neurons.[8] The presence and persistence

of central sensitization affects both disease prognosis and effectiveness of therapy in chronic pain conditions. More extensive spread of central sensitization (generalized hyperalgesia) is associated with more pain. When central sensitization is present, therapy targeting only the source of nociception (the disease site) will be relatively ineffective. Thus drug treatment modulating the sensitization of the central nervous system need to be instituted. Examples of agents achieving this are gabapentinoids and antidepressants. Secondly, the state of descending central pain modulation must also be taken into account. If there is a pronociceptive (facilitatory) shift in central pain modulation, this has a negative effect on prognosis and requires specific treatment strategies.[21]

4) Is altered central processing (still) dependent on peripheral nociceptive drive? If altered central processing becomes independent of peripheral nociceptive drive this further worsens the prognosis for controlling pain, and therapies aimed at controlling the nociceptive input from the source of disease are highly prone to failure. In this context, specific treatment dealing with altered central pain processing is mandatory e.g. gabapentinoids and antidepressants.[18]

Implications

In summary, increasing evidence shows that (ongoing) nociceptive input results in altered central pain processing and should be taken into account in the management of chronic pain. However, knowledge is lacking on how chronic painful inputs leads to altered central pain processing, and how this is influenced by disease progression and therapeutic interventions. Hence, the key to better treatment of chronic pain is measuring or visualizing the changes in the central nervous system – or neuroplasticity – that accompany the development and existence of chronic pain conditions. Together with measurements before and after treatment, the introduction of such systematic mechanism-orientated diagnostics will provide the basis for optimization of treatment indications and schedules.

A SYSTEMATIC MECHANISM-ORIENTATED APPROACH TO DIAGNOSING ALTERED PAIN PROCESSING IN CHRONIC PAIN

Quantitative sensory testing (QST), electroencephalography (EEG) and (functional) magnetic resonance imaging ((f)MRI) have increasingly been used in chronic pain disorders to describe changes in structure and function of the central nervous system. In the next paragraphs we will give a short introduction to QST, EEG and (f)MRI and their use in chronic pain conditions.

Quantitative sensory testing

The basis for QST was laid by Ulf Lindblom in the 1950s.[22] He was one of the first to describe the use of physiologic stimulation of the peripheral afferent unit in animals to test sensory processing. Later on he applied his experience in patients with sensory abnormalities i.e. chronic pain, which was the start of the use of QST in humans.[23]

QST gives clinicians and researchers the opportunity to study abnormalities in the sensory system and characterize mechanisms underlying pathologic pain disorders. Compared to bedside clinical tests, QST is reliable and quantifies both the test stimulus (i.e. heat or pressure) and the patient's response (i.e. pain).[24,25] Somatosensory evoked responses to electrical, mechanical, thermal or chemical test modalities are involved in QST.[26] The stimulus is applied in a systematic fashion to an anatomical site (skin, muscle, joint or viscera like the esophagus or sigmoid). Stimulus intensity is gradually increased until the subject reaches a predefined sensory threshold (e.g. sensation or pain). By using multiple stimuli with differing intensities it is possible to construct a stimulus-response relationship (or curve) characterizing the subjects' state of pain processing. This stimulus-response relationship is particularly useful as it also involves suprathreshold stimulation, particularly relevant to clinical pain. Measurements at the affected site or sites more distant are used to differentiate between signs of peripheral and (spinal or supraspinal) central sensitization.

Descending pain modulation ('pain inhibits pain', a response to a noxious stimulus is inhibited by another noxious stimulus) is measured using the conditioned pain modulation paradigm (CPM, formerly known as diffuse noxious inhibitory controls or DNIC). In the case of CPM a test stimulation is applied (e.g. pain threshold, pain score), afterwards a conditioning stimulus is applied (e.g. cold pressor task via ice water bucket immersion) and then again the test stimulation is applied. The difference between the two test stimuli signals the size of inhibitory or facilitatory descending modulation. When central sensitization is present descending modulatory mechanisms often fail, due to a decreased activity in the inhibitory pathway of the spinal cord and an increase in facilitatory pathway activity, resulting in a further increase in pain (Figure 1).[27,28] QST is increasingly used to compare pain sensitivity before and after interventions for patients and healthy controls in acute and chronic pain disorders.

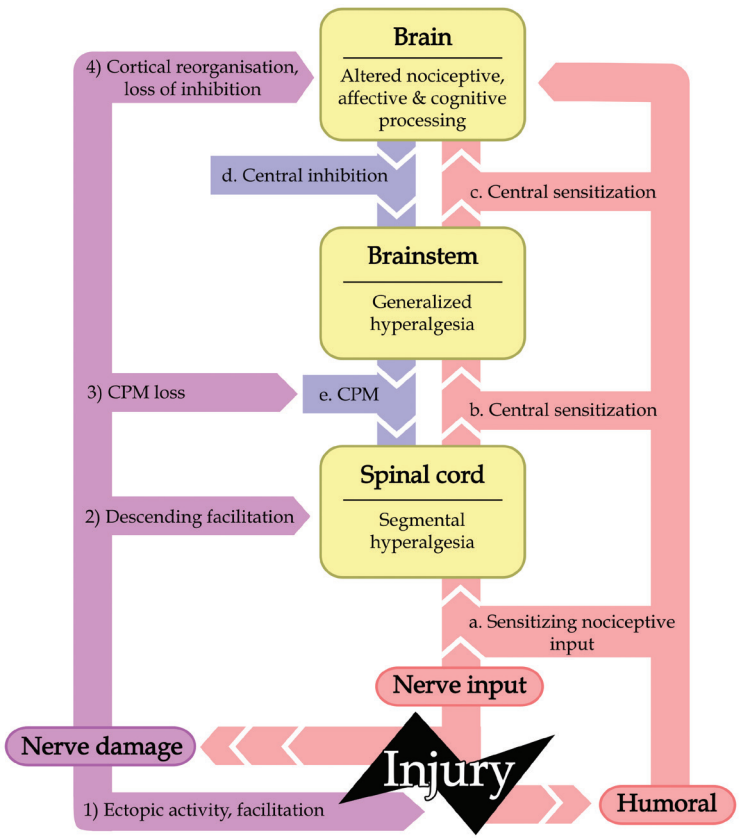
Electroencephalography

Electroencephalography (EEG) is the recording of electrical brain activity, generated by synchronous activity of thousands of millions of neurons in the cortex. Neural networks are usually randomly active at any given time in a resting state, and can be synchronized in response to an external stimulus. Therefore, EEG can be used in chronic pain conditions to study the brains' default state reflected by the resting state EEG (static element) and

brain activity due to external stimuli reflected by event related or evoked brain potentials (dynamic element).[29] As early as 1953, the EEG was already being studied in patients with pain due to peptic ulcers and functional gastric disorders by Kirschbaum and colleagues.[30] Their study is an early example of the recognition of the brain-gut axis as a possible substrate for visceral pain syndromes. Although the use of EEG can be demanding and complex, this technique is a potentially useful noninvasive method for clinical practice. EEG has a poor spatial resolution, but superior millisecond-range temporal resolution compared to other neurodiagnostic instruments such as positron emission tomography (PET) or fMRI, enabling direct measurements of neuronal processing.[29]

FIGURE 1

Summary of the views presented above regarding the mechanisms underlying pain



This figure illustrates the concept of spread of altered central pain processing (progression marked via letters) following ongoing nociceptive input due to tissue and nerve damage (progression marked by numbers). This figure is based on the original figure of ref 18.[18]

Resting state electroencephalography

The resting state EEG is commonly analyzed by transforming data from the time domain into the frequency domain. Spontaneous brain activity in the frequency domain is divided into different frequency bands (delta = 1-3.5 Hz, theta = 3.5-7.5 Hz, alpha = 7.5-13 Hz, and beta = 13-32 Hz). The awake human brain activity recorded during rest is typically dominated by oscillations in the alpha frequency band. This dominant alpha activity is most prominent over parietal and occipital cortices, and is largest when the eyes are closed.[31] Recent developments in cognitive neuroscience suggests that alpha activity reflects selective cortical inhibition, rather than neural idling.[32]

Alterations in the brains' default state as reflected by resting state EEG, particularly in the alpha band, have been observed in multiple studies in various chronic pain conditions. Typically these changes consist of a shift of peak alpha or theta frequency to lower frequencies and/or a reduction in alpha or theta power.[33-35] It seems unlikely that alpha activity is directly related to the pain experience, as a correlation between pain intensity and alpha power is absent.[35]

Evoked brain potentials

Event-related potentials or evoked potentials (EPs) are voltage polarity changes in the EEG time-locked to the onset of an external stimulus. They reflect the summed activity of postsynaptic potentials produced when a large number of similarly oriented neurons fire in synchrony while processing information.[36] EPs are traditionally extracted from the EEG by averaging similar repetitive stimuli within a stimulus block. Human EPs can be divided into two parts. The early components peaking roughly within the first 100 milliseconds after stimulus presentation are termed 'sensory' or 'exogenous' as they depend largely on the physical parameters of the stimulus. In contrast, later components of EPs reflect the manner in which the subject evaluates the stimulus and are termed 'cognitive' or 'endogenous' EPs as they examine information processing.[37] Alterations in evoked potentials are traditionally studied in the amplitudes and latencies of the (positive and negative) potential peaks, and can also be studied in the time frequency domain.[38]

In order to obtain evoked potentials that are specific to nociceptive input, such input should be the result of physiological processing of nociceptive stimuli, i.e. involving selective activation of nociceptive Aδ/ C-fibers in the periphery and recording resultant EPs generated in the cortex.[39] Brain mapping studies have established a positive relationship between the intensity of pain reported to nociceptive selective laser stimuli and EP amplitude.[40] In the context of evoked EEG studies, it must be noted that the experimental visceral electrical stimulation of large and small peripheral afferents that is generally applied to different gut segments is painful but not nociception specific.[41] Whether EPs resulting from stimuli entirely selective for nociceptive peripheral afferents

represent the experience of pain or a more generalized response of heightened attention or arousal to afferent stimuli is current topic of debate.[40,42,43] Mouraux and Lannetti demonstrated that laser-evoked EEG responses reflect neural activities equally involved in processing nociceptive and non-nociceptive sensory inputs.[42] Thus, a stimulus entirely selective for nociceptive peripheral afferents does not imply that the elicited brain activity is nociception specific. However, even if EPs reflect neuronal activities that are unspecific for the nociceptive system, their generation still relies on the consequences of nociceptive activation and resultant changes in central nervous system state at both peripheral and central levels.[42]

(functional) Magnetic resonance imaging

(f)MRI has been increasingly used to describe brain activity and structural changes in chronic pain disorders. (f)MRI uses different techniques to measure functional brain activity. Changes in oxygenated and deoxygenated hemoglobin can be measured by the blood oxygenation level dependent technique (BOLD).[44] By this technique the change in oxygenation (reflecting neuronal activity) in different areas of the brain can be estimated. Recently diffusion tensor imaging (DTI) has been used to measure changes in gray and white matter microstructure, and connectivity between brain areas.[45] Other functional techniques are signal enhancement by extravascular water protons (SEEP) and arterial spin labeling (ASL) which allows the measurement of whole brain cerebral blood flow.[46,47] Taken together, the (f)MRI techniques allow assessment of the neural activation induced by stimuli like pain, and the structural neuroplastic changes induced by a long-lasting pain input. Compared to QST and EEG the advantage of (f)MRI is that it can take into account anatomy and can quantify the area of neuronal activity. The downside of the technique is that it is difficult to assess whether neural activity has a facilitatory or inhibitory effect on the pain processing. The main use for fMRI lies in anatomical resting state and activation studies.[48] Increasing evidence from studies using these tools has provided us with more information on central pain processing and how it can be influenced by disease progression and treatments.

Clinical diagnostics of pain processing

For implementation in the clinical context, a suitable tool to diagnose altered pain processing in chronic pain should fulfill the following criteria.[18]

1) The tool should be validated and suitable for a clinical setting with a minimal burden for the patient. Measurements should be easy to reproduce and stimuli should be standardized so data can be compared between patients and populations. A tool that is easy to use can be used in an outpatient setting and has a low burden, increases patient compliance and makes the method more practical for clinical use.

2) The tool should reveal altered pain processing for both superficial and deep tissue stimulation. Differences in deep and superficial tissue stimulation may help discriminate between somatic and visceral origin of pain and the extent of central sensitization (e.g. somato-somatic, viscero-visceral and viscero-somatic spread of hyperalgesia).
3) The tool should contain static (pain sensitivity) and dynamic (pain modulation) elements. Static measurements provide insights into basal pain sensitivity (e.g. central sensitization) and dynamic measurements test how the body actively modulates nociceptive input.
4) The tool should sensitively assess changes in sensitization of pain processing as well as alterations in state of cortical/descending modulation. In the context of sensitized signal processing by the central nervous system, this will help differentiate e.g. between a situation of ongoing nociceptive input directly sensitizing central processing and pronociceptive alterations of descending nociceptive control by brainstem and brain (Figure 1).
Application of such a holistic approach to chronic pain is the basis for systematic mechanism-orientated pain management enabling: 1) diagnosis and prognosis of chronic pain; 2) rationale for treatment choice and responder identification; and 3) monitoring of chronic pain and its treatment.[18]

EVIDENCE FOR A SYSTEMATIC MECHANISM-ORIENTATED APPROACH TO CHRONIC PAIN

In the next paragraphs we will focus on QST, EEG and (f)MRI research documenting the reality of altered pain processing in chronic visceral pain disorders such as chronic pancreatitis and thus providing further evidence for the feasibility of achieving a systematic mechanism-orientated approach in clinical practice.

What is the source of nociception?

In the literature the following pathophysiological mechanisms have most commonly been suggested as causes of pain in chronic pancreatitis: 1) increased intrapancreatic pressure within the parenchyma and/or pancreatic duct causing tissue ischemia (due to pancreatic duct strictures and stones); 2) inflammation of the pancreas; and 3) pancreatic and extrapancreatic complications (i.e. pseudocysts, bile duct/duodenal strictures and peptic ulcers).[49-53] The exact pathophysiology of chronic pancreatitis is still unknown and which mechanisms starts first are still subject to debate i.e. are duct strictures caused by tissue ischemia or inflammation or both?

Is nociceptive transmission altered?

In the past years, increasing evidence has been published regarding altered nociception

transmission (e.g. nerve damage, peripheral sensitization) in chronic pain patients like chronic pancreatitis.[12,16,28,54] In chronic pancreatitis transmission of nociceptive input from the pancreas to the spinal cord can be altered and influenced by lesions in intrapancreatic and peripheral nerves, as described in histological studies.[55,56] These changes are comparable with other neuropathic pain disorders.[8,57] Not only an increase of excitability of nerves innervating the pancreas, but also structural changes of nerves in the pancreas may be a part of the problem. Hence, hypertrophy, increased neural density and neuritis of intrapancreatic nerves have been reported to be associated with pain in chronic pancreatitis patients.[58,59] Ongoing nociceptive input due to the inflammation of the pancreas and its local complications may lead to nociceptors becoming more sensitive to further stimulation. This peripheral sensitization may be caused by up regulation of nerve growth factors, brain-derived neurotrophic factors and proinflammatory cytokines, and lead to increased pain intensity.[60,61] Pancreatic neuroplasticity (remodeling) and peripheral sensitization (increased excitability) will increase the nociceptive drive to the central nervous system resulting in an increased reaction of pain transmitting neurons (increase of pain).[59] Finally, this process may result in spontaneous nociceptive activity without the presence of nociceptive inputs and to an aggressive increase of pain signals to the spinal cord.[16,62]

Is central pain processing altered?

Quantitative sensory testing – chronic pancreatitis

Increasing evidence has been published on segmental and generalized hyperalgesia and referred pain as a sign of spinal and supraspinal central sensitization in chronic pancreatitis. Accordingly, decreased pain thresholds (i.e. hyperalgesia) for somatic stimulation in dermatomes near and distant to the pancreas in chronic pancreatitis patients are evident.[7,11,13,28,54] In agreement with this, other studies report increased areas of referred pain to electrical stimulation of viscera of upper gastrointestinal organs and decreased pain thresholds to visceral stimulation of the rectosigmoid.[63,64] These results suggest that peripheral visceral and somatic nerves converge at spinal levels in the central nervous system to elicit (somatic) referred pain as a sign of spinal central sensitization.[65,66] Failure of descending inhibitory pain modulation (CPM) has also been observed in chronic pancreatitis patients.[11,25,27,28,54] Probably this is due to a decreased activity in descending inhibitory pathways to the spinal cord as well as an increase in facilitatory activity projecting to the posterior spinal horn.

Quantitative sensory testing – visceral pain conditions

Similar to chronic pancreatitis, sensitization of the central nervous system is seen in other inflammatory visceral pain conditions e.g. esophagitis and inflammatory bowel

disorders, where it can be local in the viscera, spreading in the surrounding area or more distant in the case of referred pain. Drewes et al showed segmental sensitization to thermal stimulation of the distal esophagus in esophagitis patients, together with a larger referred somatic pain area to mechanical stimulation, both reflecting central sensitization.[67] Comparable results were found in ulcerative colitis and Crohn's disease patients, who showed decreased pain thresholds to balloon dilation of the colon or rectal stimulation again suggesting visceral hypersensitivity as a sign of central sensitization.[68-70] Evidence for descending counter-regulatory mechanisms has been described for patients with peptic ulcer and Crohn's disease, both of whom showed hypoalgesia to visceral stimulation as a sign of effective tonic descending inhibition.[71-73]

Clinical application of quantitative sensory testing

In addition to characterization of the pain mechanisms underlying visceral pain disorders, QST has been used to study the effects of pain treatment on pain processing. In a study of S-ketamine, a noncompetitive NMDA receptor antagonist whose activity is related to central sensitization, infusions in chronic pancreatitis patients were associated with a short-lasting increase in pain pressure thresholds, without a reduction in clinical pain. However, this study was not powered on clinical endpoints and had a short infusion time.[11] Another study showed that pregabalin reduced clinical pain in chronic pancreatitis and was associated with a moderate antihyperalgesic effect. Interestingly patients treated with placebo also showed a reduction in clinical pain, but this effect came without changes in pain thresholds measured by QST.[12,14]

The role of disease progression in chronic pancreatitis and how it is influenced by interventions has not been well studied. Just one exploratory study in chronic pancreatitis patients showed a relation between a more severe disease stage and lower pain thresholds (more hyperalgesia) compared to a moderate disease stage and healthy controls.[28] Interestingly, a study in chronic pancreatitis patients after pain-relieving pancreatic surgery showed that patients with a poor pain outcome after surgery showed more central sensitization and more pronociceptive descending pain modulation compared to patients with a good pain outcome and healthy controls.[74]

To summarize: chronic pancreatitis and other abdominal visceral pain syndromes show similarities in pain mechanisms and physiology. In the area of tissue damage and its surrounding tissue there is typically hypersensitivity to all kinds of different stimuli as signs of segmental hyperalgesia. When pain is ongoing, tissues more distant of the area of injury also become sensitized as (generalized hyperalgesia) as a sign of spreading central sensitization. Failure of counter-regulatory mechanisms such as DNIC, measured via e.g. CPM, also leads to hyperalgesia and pain increases. Treatments aimed at central pain mechanisms may reduce pain and hyperalgesia in such patients. Evidence

regarding the role of disease progression and treatments aimed at reducing pain and central sensitization is still scarce. However, it is evident that QST can play a useful role in quantifying pain processing and its impact on clinical pain before and after pain treatment.[75,76]

Resting state electroencephalography – chronic pancreatitis

Olesen et al reported an increase in amplitude strength in the theta and alpha band in patients with chronic pancreatitis compared to healthy controls, reflecting slowed EEG rhythmicity in patients with chronic pancreatitis compared to controls.[77] Another study demonstrated a significant shift toward lower frequencies in patients with chronic pancreatitis compared with healthy controls.[34] This was observed as a decrease in peak alpha frequency (PAF) over all scalp electrodes. Interestingly, these changes correlated with duration of pain, further supporting alterations in resting state EEG as a potential biomarker in chronic pain conditions.

The mechanisms underlying these observations are still poorly understood. One hypothesis is that of thalamocortial dysrythmia (TCD), where damage or lesions to afferent neural pathways results in deafferentation and a decrease in excitatory input to the thalamic relay cells. This results in disfacilitation and cell membrane hyperpolarization due to activation of T-type calcium channels. In this hyper-excitatory state thalamic relay neurons fire low threshold spike bursts and the normal thalamo-cortical rhythmicity is disturbed.[29] Application of drugs that interfere with T-type calcium channel function may prevent low frequency bursting, reverse TCD, and alleviate pain in conditions with underlying TCD. Thus resting state EEG may be of value not only as a potential biomarker for chronic pain progression via shifts in oscillatory activity, but also in treatment decisions and evaluation via identification of TCD. Another hypothesis is based on recent experiments indicating that the phase of alpha activity modulates perception and that alpha oscillations are produced by periodic pulses of inhibition. It was suggested that posterior alpha oscillations provide a mechanism for prioritizing and ordering unattended visual input according to 'relevance' or saliency.[32] However, it is unclear whether the proposed role of alpha activity can be generalized to other modalities, such as the somatosensory and nociceptive system.

Evoked brain potentials electroencephalography – chronic pancreatitis

Dimcevski et al recorded EPs after stimuli given with a constant current electric stimulator at the three different sites of the upper gastrointestinal tract. Patients with chronic pancreatitis had a significantly decreased latency for the N1 and P1, while N2 latency was borderline significant compared to healthy subjects. No differences were found in the amplitudes of the N1, P1, and N2 potentials.[63] In another study using evoked visceral

pain of the upper gastrointestinal tract, patients showed higher activity than controls in the theta band, with prolonged persistence of the signal and at lower frequency (4.4 Hz in patients compared to 5.5 Hz in controls).[10] In a second study, patients with chronic pancreatitis showed hyperalgesia to electrical stimulation and prolonged latencies of early visceral EPs components in the frontal region of the cortex compared to healthy controls. Additionally, scalp distributions of EP amplitudes were more scattered and more posteriorly located in the patient group.[27] As the changes in cortical processing were correlated to the pain this further validates the findings. To date, no comparable data are available for other types of abdominal focus-related chronic pain.

Clinical application of electroencephalography

Studies using EEG to identify patients who may benefit from treatment strategies targeting central pain mechanisms are limited. Graversen et al studied the resting state EEG after a three week regimen of pregabalin or matching placebo in patients with chronic pancreatitis.[78] Patients in the pregabalin group showed a significant increase in theta activity after pregabalin treatment, while no changes were observed for the other frequency bands, nor were any changes found in the placebo group. The authors concluded that quantitative pharmaco-EEG can be used to monitor central analgesic mechanisms of pregabalin and may in the future be used to predict treatment effects.[78]
To summarize, studies in chronic visceral pain have investigated both the resting state as well as the evoked EEG. The use of multiple analysis techniques and different stimulation methods makes these results difficult to compare. Alpha activity in the resting state EEG has been shown to be affected in multiple chronic pain states including chronic pancreatitis, suggesting a change in the default state of the brain as a result of chronic pain. Pain-evoked EEG studies in chronic pancreatitis patients demonstrate alterations in dynamic pain processing reflected by prolonged latencies of visceral EPs and higher theta activity with prolonged persistence of the signal at a lower frequency during experimental visceral pain. Taken together, these EEG findings further support the concept that chronic visceral pain conditions such as chronic pancreatitis are associated with significant and ubiquitous alterations in resting state and evoked central nervous system processing, both nociceptive and non-nociceptive.

(functional) Magnetic resonance imaging

The cortical and subcortical structures that are involved in visceral pain are the thalamus from which signals further ascend to different parts of the brain i.e. the limbic system (insula, cingulate cortex and prefrontal cortex), the primary (discriminating pain) and secondary (recognizing and remembering pain) somatosensory cortex.[29] In particular the insula has an important function in pain perception from the gut.[79] The functional

relationship between these areas was described with DTI for healthy controls who underwent rectal distension.[80] Important areas for pain experience, influenced by cognitive, affective and emotional components, are processed in the limbic system. Other structures involved are: the amygdala, periaquaductal gray matter, reticular formation and hypothalamus. These structures are mostly related to pro- and antinociceptive control such as descending pain control.[81]

(functional) Magnetic resonance imaging – chronic pancreatitis

A MRI study with DTI in chronic pancreatitis patients showed increased diffusivity in grey matter regions of the insula and cingulate cortex suggesting microstructural changes of pain associated brain areas. These observations appeared to be directly correlated to the pain experienced by patients. Another MRI volumetry chronic pancreatitis study supported these findings and showed cortical thinning in similar brain areas (the limbic system).[82] Brain areas that are associated with descending pain modulation e.g. the cingulate cortex, hypothalamus and periaqueductal grey matter showed cortical thinning in some studies with chronic pancreatitis patients. These results might explain impaired descending inhibition in chronic pancreatitis.[27,82] Overall, in chronic pancreatitis patients different brain areas that are involved in visceral pain processing showed a decrease in cortical thickness. Whether these changes are due to chronic pain and how these changes influence pain processing is unknown at the moment.

(functional) Magnetic resonance imaging – visceral pain conditions

Studies in other abdominal visceral pain syndromes are scarce. However, similar results to studies in chronic pancreatitis were found in patients with inflammatory bowel disease when they were compared to healthy controls.[83]

Clinical application of (functional) magnetic resonance imaging

At present there are no studies using (f)MRI to observe therapeutic effects or disease progression in chronic pancreatitis.

To summarize: similarly to EEG studies, (f)MRI studies have shown for chronic pancreatitis patients and other visceral pain syndromes that changes in brain activity are present particularly in areas that are related to pain processing such as the limbic system, hypothalamus and periaqueductal regions. However the role of pain in these changes and how this influences pain perception is poorly understood at the moment.

Is altered central processing (still) dependent on peripheral nociceptive drive?

Central sensitization manifest as spreading hyperalgesia can ultimately become independent of peripheral nociceptive input and no longer respond to treatments

targeting the source of nociception and/or achieving peripheral deafferentation i.e. nerve blocks and opioids. Changes in central pain processing independent of peripheral nociceptive input were supported by a study involving chronic pancreatitis patients who had a splanchnic denervation to reduce pain, but where ca. 75% continued to experience painful and exhibit widespread hyperalgesia (four years) after a technically successful procedure, suggesting real central autonomy.[54,84] Further literature on the reversibility of central sensitization is scarce. One study described two different groups of patients with osteoarthritis after hip replacement surgery, one that showed reversibility of hyperalgesia and a descending inhibitory modulation deficit and another group that had ongoing pain without changes in hyperalgesia and no changes in central inhibition suggesting the presence of central autonomy.[85]

IMPLEMENTING A SYSTEMATIC MECHANISM-ORIENTATED APPROACH TO CHRONIC PAIN IN CLINICAL PRACTICE

Source of nociception

QST performed at the site of the nociceptive focus can help identify the source of nociception and provide insight into the nature and aggressiveness of the nociceptive input involved (e.g. visceral pain). EEG and (f)MRI diagnostics have no role in this context.

Altered nociceptive transmission

QST performed close to the site of nociception can be used to help diagnose peripheral sensitization (local, primary hyperalgesia, usually thermal) and nerve damage (classically thermal hypoalgesia and hypoesthesia in the territory of the nerve in question).[86-88] Theoretically, evoked potential EEG studies (EPs) could be used to quantify alterations in nociceptive transmission. However, most EP studies only involve large fiber non-nociceptive somatosensory processing; there are only a few such studies involving nociception-relevant small fibers (e.g. laser EPs).

Role of quantitative sensory testing in describing altered central pain processing

QST measured close and distant to the site of pain allows differentiation between segmental (spinal central sensitization) or generalized (supraspinal central sensitization) hyperalgesia. Stimulation of different tissues (e.g. electrical skin stimulation, mechanical stimulation of muscle by pressure algometry) can further help understand the source of pain and spread of associated altered pain processing. Dynamic QST measurements such as the conditioned pain modulation (CPM) paradigm are helpful in diagnosing shifts in descending nociceptive modulation.

Is altered central processing (still) dependent on peripheral nociceptive drive?
In this case, central sensitization is present but no longer dependent on ongoing nociceptive input. Thus (trial) treatments aiming to deafferent the nociceptive source (e.g. nerve block or nerve transection) will not be accompanied by changes in central pain processing (e.g. spreading hyperalgesia) as measured by QST. As flanking – mainly experimental – procedures, EEG and (f)MRI have made it possible to directly demonstrate cortical reorganization, altered connectivity and modulation in chronic pain conditions.

Clinical use

Diagnostics

At our institution, QST has proven useful to diagnose and monitor changes in pain processing accompanying chronic pain. Our research and clinical experience suggest that implementation of a systematic mechanism-orientated approach to pain based on a simple diagnostic QST is both feasible and desirable in clinical pain practice. To this end we have instituted a simple QST screening paradigm, which all difficult chronic pain patients undergo (the Nijmegen-Aalborg Screening QST (NASQ)).[18] The NASQ paradigm includes four measurement points measured bilaterally (close and distant to the site of pain, thus providing topographical information), two stimulation modalities (electric and pressure stimulation) and a CPM paradigm (cold pressor task). Details are provided in Table 1.[18]

TABLE 1

The Nijmegen-Aalborg Screening QST paradigm

Standard QST	
Sites (bilateral)	Trapezius muscle, thenar eminence, rectus femoris, abductor hallucis, site of pain
Thresholds	Pressure pain, electric detection, electric pain detection, electric pain tolerance
Conditioned Pain modulation	
Sites	1. ice water bucket (non-dominant hand) 2. thresholds on rectus femoris
Thresholds (before ice water/180s after)	Pressure pain, electric pain tolerance

Quantitative sensory testing (QST) measurements to detect central sensitization and pro- or anti-nociceptive shifts in descending pain modulation.[18]

The NASQ paradigm is well accepted by patients, easy to perform and learn, and can be completed within 30 minutes. Thermal QST testing can be added to test specifically for peripheral nerve damage.[18,89]

Regarding clinical use of EEG and (f)MRI in chronic pain, the literature remains scarce. Furthermore both investigations are onerous, time consuming and expensive. Therefore we do not at present recommend their use in daily clinical practice for chronic pain patients, reserving these techniques for research.

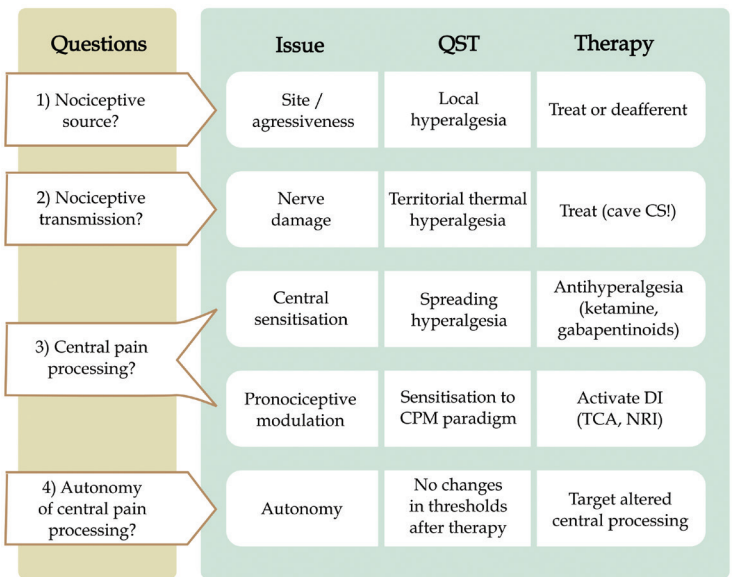
Therapeutics

The new approach to pain in chronic pancreatitis presented here allows for holistic and systematic management of chronic pancreatitis pain. Such a systematic mechanism-orientated approach not only facilitates the diagnosis and prognosis of chronic pain, it also provides the possibility of monitoring signs of chronic pain progression. As such, it forms the basis for more rational choice of treatment options to maximize treatment response, together with subsequent ongoing monitoring of effectiveness of chronic pain treatment.

Figure 2 provides a summary of our systematic mechanism-orientated approach to chronic pain, such as pancreatitis pain, as implemented at our institution. The scheme is based on the literature discussed in this review and our own clinical experience and practice.

FIGURE 2

Schematic for systematic mechanism-orientated approach to chronic pancreatitis pain



Autonomy means that alterations in central pain processing have become independent of peripheral nociceptive drive. 'CS' is central sensitisation, 'CPM' is conditioned pain modulation, 'DI' is descending inhibition, 'TCA' is tricyclic antidepressant, 'NRI' is noradrenaline reuptake inhibitor.[21] This figure is based on the original figure of ref 18.[18]

CONCLUSIONS

Intense abdominal pain is the dominant feature of chronic pancreatitis. In this review we propose a new systematic mechanism-orientated approach to the chronic pain of chronic pancreatitis. Multiple studies support that pain in chronic pancreatitis is similar to other visceral pain syndromes such as inflammatory bowel disease. Increasing evidence has shown that changes in central pain processing are present and comparable in chronic pancreatitis and other abdominal visceral pain syndromes. The data suggest that changes in pain processing due to chronic visceral pain are common and necessitate a targeted and mechanism-orientated diagnostic and therapeutic approach. This management approach needs to be holistic, including not only traditional treatments addressing the pancreas as a nociceptive source, but also specifically searching for – and therapeutically targeting – alterations in central nervous system processing of pain.

As shown in this review, QST, EEG and (f)MRI can be useful diagnostic instruments to analyze central pain processing and help us in finding optimal mechanism-orientated treatments for pain in chronic pancreatitis and other chronic visceral pain syndromes. Future research should define the presence and pattern of altered pain processing for specific chronic pain disorders and compare this with a healthy population using diagnostic tools such as QST, EEG and fMRI. Apart from characterization of hyperalgesia and descending pain modulation further questions need to be addressed. How does hyperalgesia develop over time? How is this influenced by disease progression and our treatments? What is the impact of gender and psychological state? Can we predict patients who are prone to chronic pain and altered central pain processing? The only way to increase our knowledge in this respect is to measure the effect of pain and nociception on central pain processing in large-scale clinical studies using QST, EEG or fMRI before and after interventions and during disease progression.[78] This will help us evaluate therapies and guide us to the proper treatment for a specific patient at a specific disease stages. Such personalized medicine is the key to improved pain treatment and may pave the way to new and more effective therapeutic approaches.

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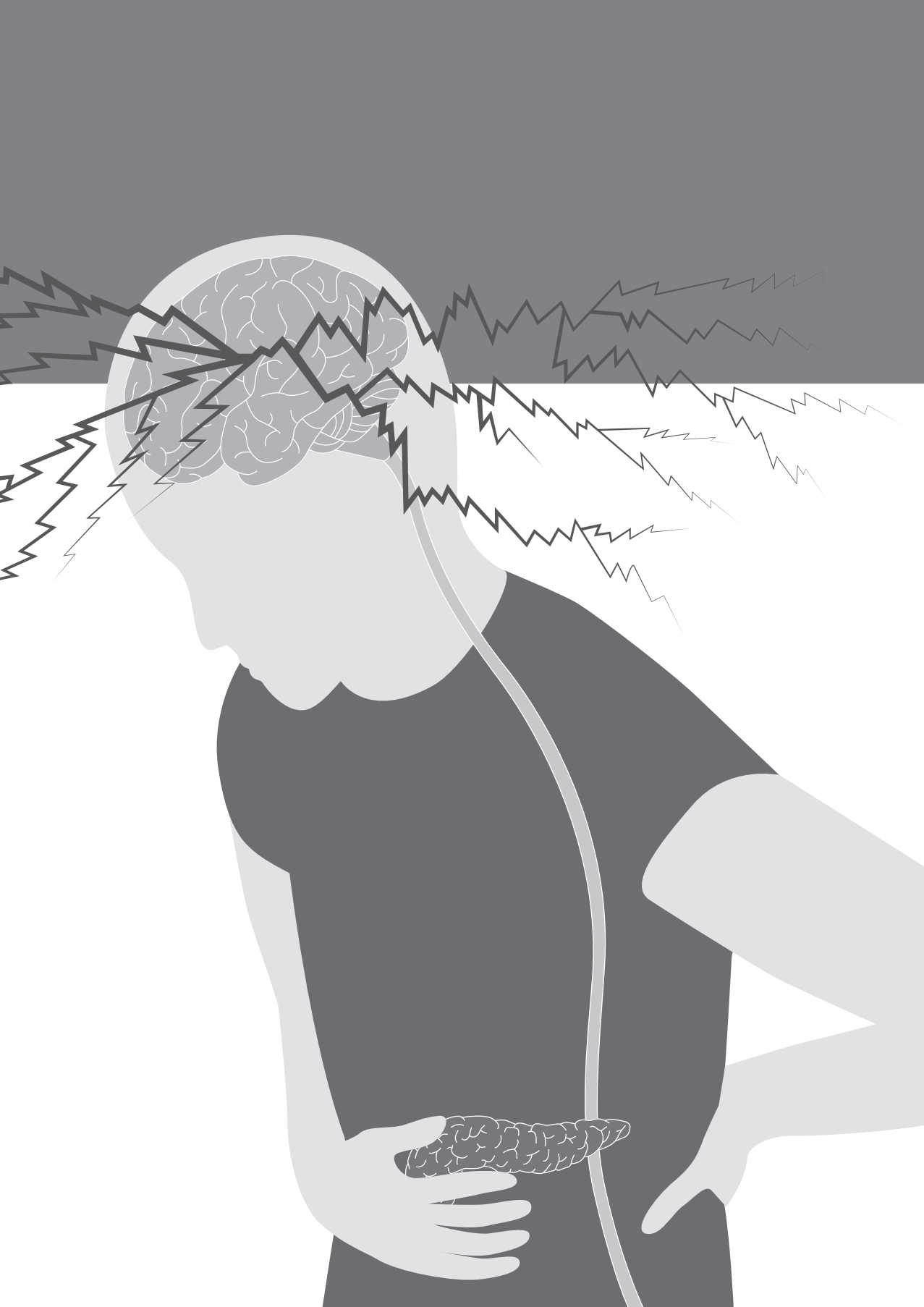


Chapter 11

Summary

SUMMARY

The aim of this thesis was to describe the central pain mechanisms underlying chronic pain in chronic pancreatitis, and to provide new insights into pain treatment in chronic pancreatitis.
Four aims were formulated and discussed in the presented chapters:

1. To identify changes in central pain processing (central sensitization) in chronic pancreatitis
2. To identify prognostic factors for altered central pain processing in chronic pancreatitis
3. To evaluate pain management in chronic pancreatitis and its relation to altered central pain processing
4. To propose a new, holistic view on pain management in chronic pancreatitis based on specific alterations in central pain processing present in the individual patient (personalized medicine)

Patients with painful chronic pancreatitis often have altered central pain processing which might be associated with abnormal brain morphology. In **chapter 2** we described the assessment of cortical thickness (a sign of structural reorganization), using a 3T magnetic resonance scanner, in brain areas involved in visceral pain processing. Brain morphology was analyzed of nineteen patients with painful chronic pancreatitis and compared with fifteen healthy individuals. Cortical thickness was assessed by using an automated method with surface-based cortical segmentation 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 based on the average amount of daily pain for one week. We found that chronic pancreatitis patients, compared with controls, had reduced overall cortical thickness ($P < 0.01$). These results were unaffected by confounders like diabetes, alcohol use, or opioid treatment (all $P > 0.05$). A similar decrease in cortical thickness was found for the chronic pancreatitis patients compared to controls for the SII ($P < 0.01$), PFC ($P < 0.05$), FC ($P < 0.001$), MCC ($P = 0.001$) and insula ($P < 0.01$). Brain areas without differences in cortical thickness between both groups were the control area, SI, ACC, and PCC (all $P > 0.05$). Cortical thickness in the affected areas correlated with pain score ($r = 0.47$, $P < 0.01$). It was concluded that chronic pancreatitis patients have reduced cortical thickness in brain areas involved in pain processing. These alterations seem to have functional significance and support the present literature from basal and clinical science on changes in central pain processing and neural remodeling. As a result of long-term, ongoing pain input to the neuromatrix,

cortical thickness might serve as a measure for overall pain system dysfunction.
Changes in spinal or supraspinal central nervous system pain processing caused by visceral nociceptive input plays an important role in chronic pain. Disease stage and progression of chronic pancreatitis were introduced as possible contributors to the extent of these changes in central pain processing in chronic pancreatitis in **chapter 3**. We divided 60 chronic pancreatitis patients into two subgroups based on the M-ANNHEIM severity index of chronic pancreatitis: 'moderate' and 'severe'. Both groups were compared with fifteen healthy controls. We compared all three groups using quantitative sensory testing for pressure pain detection and tolerance thresholds, and electric pain detection and tolerance thresholds, measured in six selected dermatomes (C5, T4, T10, T10 BACK (dorsal), L1 and L4). Also the conditioned pain modulation response to a cold pressor task was measured. Firstly, we compared the 'severe' with 'moderate' chronic pancreatitis patients and showed that the 'severe' chronic pancreatitis patients had overall lower pressure pain detection ($P < 0.001$), electric pain detection ($P < 0.05$) and electric pain tolerance thresholds ($P < 0.05$) than 'moderate' chronic pancreatitis patients. Secondly, we compared the 'severe' chronic pancreatitis patients with healthy controls and showed that the 'severe' chronic pancreatitis patients had lower pressure pain detection ($P = 0.001$), electric pain detection ($P < 0.01$) and electric pain tolerance thresholds ($P < 0.05$) results when compared with healthy controls. No significant differences were found between groups for the pressure pain tolerance thresholds. Finally, there were no significant differences between 'moderate' chronic pancreatitis patients and healthy controls for all measured thresholds. These results suggest variations in supraspinal central sensitization (central pain processing), which is related to disease stage: more severe disease exhibits more central sensitization. Descending pain modulation, measured by the conditioned pain modulation was much higher (better) in the healthy controls compared to all chronic pancreatitis patients ($P < 0.0001$), suggesting that central pain processing is affected not only for ascending mechanisms, but also for descending mechanisms. Overall, these results suggest that central sensitization is affected by disease stage in chronic pancreatitis and should be taken into account when managing pancreatitis pain.
In **chapter 4** we evaluated the relationship between pain processing and pain outcome after pancreatic duct decompression or pancreatic resection in patients with chronic pancreatitis. Quantitative sensory testing was used to measure electric pain detection and electrical pain tolerance thresholds in two dermatomes (C5 and L4) distant from the pancreas in 48 chronic pancreatitis patients. Inhibitory descending pain control mechanisms were assessed using the conditioned pain modulation paradigm. Chronic pancreatitis patients were divided into two subgroups based on their pain outcome after surgery: 'poor pain outcome' (visual analogue scale (VAS) score greater than 30) and 'good pain outcome' (VAS score 30 or less). Chronic pancreatitis patients were

compared with fifteen healthy controls. Overall, chronic pancreatitis patients had lower electric pain detection and tolerance thresholds and a lower CPM response compared to healthy controls ($P < 0.05$). Patients with a poor pain outcome after surgery had lower electric pain detection thresholds than patients with a good pain outcome ($P < 0.01$). There was a negative correlation between VAS score and electric pain detection ($rs = –0.45$, $P < 0.05$) and electric pain tolerance thresholds ($rs = –0.46$, $P < 0.05$), and conditioned pain modulation response ($rs = –0.43$, $P < 0.01$) in chronic pancreatitis patients. Based on these results we concluded that chronic pancreatitis patients exhibit altered central pain processing after pain-relieving surgery compared to healthy controls. Chronic pancreatitis patients with a poor pain outcome after surgery showed more central sensitization and more pronociceptive descending pain modulation compared with chronic pancreatitis patients with a good pain outcome after surgery. These results suggest that these changes have become relatively independent of peripheral nociceptive input. The observed differences should be considered when managing persistent pain after pain-relieving surgery for chronic pancreatitis and should be dealt with before a new surgical intervention is considered.

As a follow-up to the studies in chapter 3 and 4, altered pain processing in chronic pancreatitis was further explored in **chapter 5**. Independence of central sensitization from ongoing peripheral nociceptive input has been suggested to be present in chronic pancreatitis patients that remain painful after successful denervation procedures of the pancreas. In these cases pain is not driven by nociception from the pancreas but is caused by persisting, autonomous changes in the central nervous system. We investigated whether bilateral thoracoscopic splanchnicectomy, performed to reduce nociceptive input in chronic pancreatitis patients, affects central pain processing. Seventeen chronic pancreatitis patients were studied preoperatively and six weeks after bilateral thoracoscopic splanchnicectomy. Pressure pain thresholds were measured, using quantitative sensory testing, before and after splanchnicectomy in a dermatome distant from the pancreas (C5) and a pancreatic dermatome (T10 BACK (dorsal)), reflecting supraspinal and spinal central sensitization, respectively. Chronic pancreatitis patients were divided into two groups based on their change in thresholds: 'hypoalgesic' patients had an increase in thresholds after intervention and 'hyperalgesic' patients had no change or a decrease in thresholds after intervention. This division was made both for the pancreatic dermatome (T10) and for the dermatome distant from the pancreas (C5). Postoperative scores on the pain numeric rating scale (NRS) were correlated to the change in pain thresholds. After splanchnicectomy, ten patients showed C5 pain pressure threshold increase (hypoalgesic), seven patients had unaltered or lower pain pressure thresholds (hyperalgesic). Preoperative pain NRS was similar between groups (median 4 vs. 5). After splanchnicectomy, NRS in the hypoalgesic group was lower (median 1 vs. 6,

P < 0.01) and NRS change greater (median -2 vs. 0, P < 0.01). Whole group NRS and C5 pain pressure thresholds changes showed a significant negative correlation (rs = 0.53, P < 0.05). This was not the case for pancreatic pain pressure thresholds. We found that an increase in pressure pain thresholds in a dermatome distant from the pancreas (C5), reflecting supraspinal sensitization, was associated with a significant reduction in pain scores postoperatively after bilateral thoracoscopic splanchnicectomy. This was not the case for the pancreatic dermatome (T10), reflecting more segmental spinal processing. These results suggest that a subgroup of chronic pancreatitis patients with chronic pain has altered pain processing that may be independent of ongoing peripheral nociceptive input, resulting in persisting pain despite bilateral thoracoscopic splanchnicectomy. If confirmed, these results indicate the importance of sensory testing for indication and management of interventional pain treatments. Also, these tests can be of prognostic value for the success of an intervention preoperatively and can be used postoperatively to measure the effect of an intervention.

Central sensitization and hyperalgesia, key phenomena in chronic pain, are associated with N-methyl-D-aspartate (NMDA) receptor activation. In **chapter 6** the effects of S-ketamine (NMDA receptor antagonist) and placebo infusion on generalized hyperalgesia and pain relief were described in chronic pancreatitis patients. We conducted a blinded crossover trial, in which ten chronic pancreatitis pain patients received S-ketamine for three hours at 2 mcg/kg/min or placebo infusion at an equivalent rate in randomized order. Clinical pain was assessed via visual analog scale (VAS) and short Dutch Language Version McGill Pain Questionnaire (sf-MPQ-DLV). Pressure pain thresholds, using quantitative sensory testing, were measured in dermatome C5, T4, T10 BACK (dorsal), L1 and L4. The sum of pressure pain thresholds was calculated before, at the end of, and one hour after infusion. Median pain before infusion was 29 mm at rest and 32 mm during activity (VAS score). Patients in the S-ketamine groups showed a significant increase in sum of pressure pain thresholds at infusion end compared to pre-infusion values (P < 0.05) and compared to the placebo group (P < 0.01). However, this effect was not sustained: the sum of pain pressure thresholds one hour after the infusion end were similar to pre-infusion values and to values in patients treated with placebo. No significant changes were observed in VAS and sf-MPQ-DLV scores during the study. S-ketamine was tolerated well by all patients. This study showed that S-ketamine infusion is more effective than placebo in increasing pain pressure thresholds in chronic pancreatitis pain patients immediately after infusion. These results confirm the acute antihyperalgesic effect of S-ketamine. Despite short-term positive effects of S-ketamine, this effect did not outlast the infusion. Still many questions remain unsolved regarding the optimal dosage, duration and route of administration to describe an optimal treatment schedule with S-ketamine. When these topics are better understood, a more prolonged effect of S-ketamine may turn out to be feasible.

Agents such as pregabalin (gabapentinoid) can be used to treat patients with neuropathic pain. Evidence from basic science and human studies has shown that chronic pancreatitis patients have abnormal pain processing that resembles the pain processing in patients with neuropathic pain disorders. In **chapter 7** we described a randomized controlled trial which compared pregabalin and placebo and its effect on pain in chronic pancreatitis patients. Sixty-four chronic pancreatitis patients were randomized in this double-blind, placebo-controlled trial to evaluate the effects of pregabalin as an adjuvant analgesic. Patients were randomly assigned to groups given increasing doses of pregabalin or placebo (control) for three consecutive weeks. The primary endpoint was clinical pain relief, based on a visual analogue scale documented by a pain diary. Secondary endpoints included patients' global impression of change (PGIC) score, changes in physical and functional scales, pain character, quality of life, and tolerability. Pregabalin, compared with placebo, resulted in more effective pain relief after three weeks of treatment (36% vs. 24%, $P < 0.05$). The percentage of patients with 'much' or 'very much' improved health status (PGIC score) at the end of the study was higher in the pregabalin than the control group (44% vs. 21%, $P < 0.05$). Changes in physical and functional scales, pain character, quality of life, and number of adverse events (mostly mild to moderate) were comparable between (the) groups. 61% of patients tolerated the maximum dosage of pregabalin and 90% tolerated the maximal placebo dosage. Medication compliance was high in both groups (> 90%). This study showed the efficacy and tolerability of pregabalin as an adjuvant analgesic for the treatment of pain in chronic pancreatitis. A dosage of pregabalin between 150 mg and 300 mg twice daily resulted in clinical significant pain reduction.

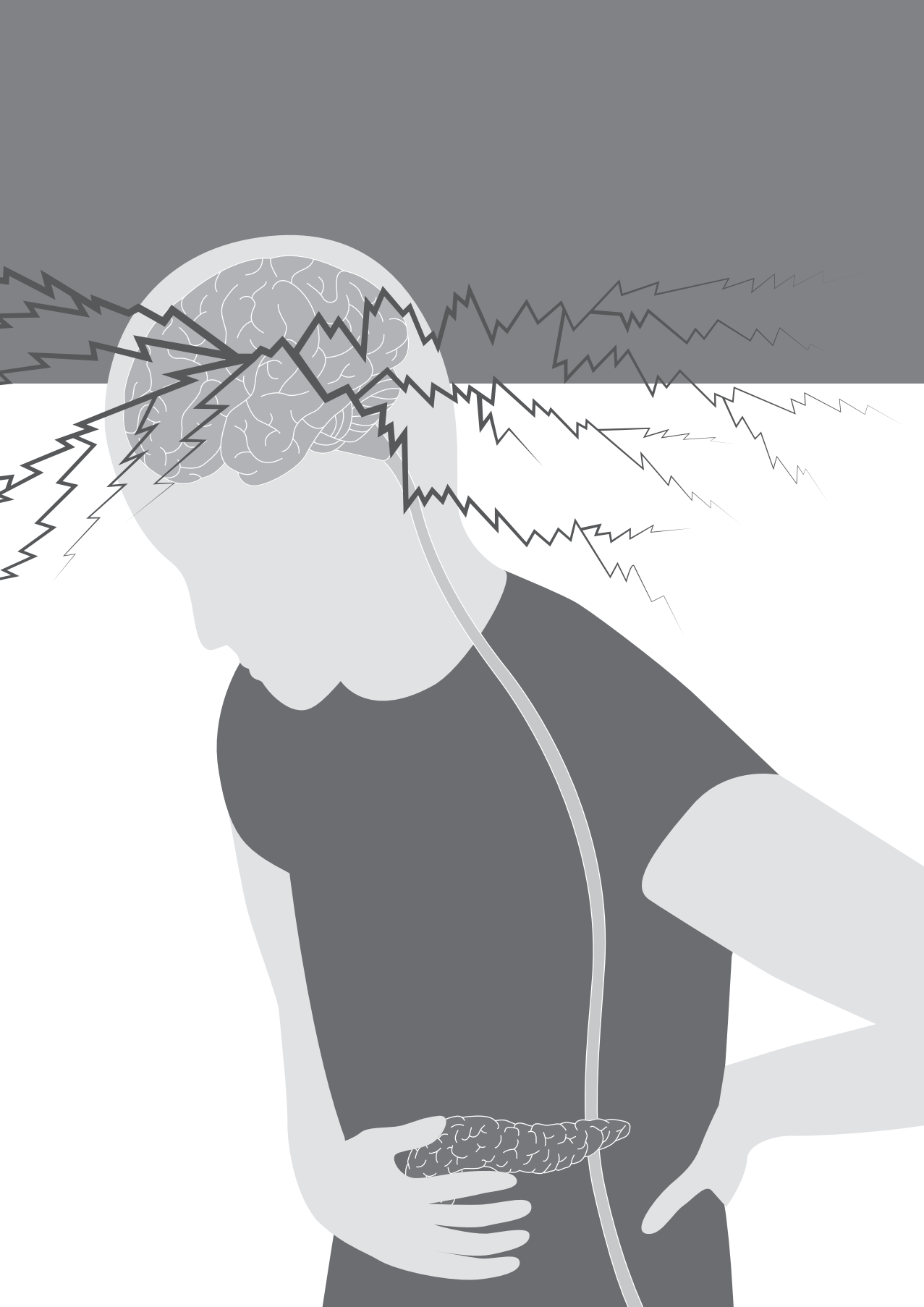
In **chapter 8** the experimental endpoints of the randomized controlled trial comparing pregabalin and placebo in chronic pancreatitis were discussed. The aim of the study was to evaluate the effect of pregabalin on pain processing in chronic pancreatitis as assessed by quantitative sensory testing. Electric pain thresholds and pressure pain thresholds were measured in six body dermatomes (C5, T4, T10, L1, L4 and T10 BACK (dorsal)). Descending endogenous pain modulation was quantified using the conditioned pain modulation (CPM) paradigm. The main effect parameter was the change in the sum of all body pain threshold values after three weeks of study treatment versus baseline values between the two treatment groups. All 64 randomized patients were analyzed. Changes in sum of pain thresholds were comparable, after three weeks of study treatment, between the pregabalin and placebo group. For individual dermatomes the change in pre and post treatment thresholds was significantly larger in the pregabalin group for electric pain detection thresholds in dermatome C5 ($P < 0.01$), for electric pain tolerance thresholds in dermatomes C5 ($P < 0.05$) and L1 ($P = 0.05$), and for pressure pain tolerance thresholds in dermatome T4 ($P < 0.01$). No differences were observed between

pregabalin and placebo regarding conditioned pain modulation. These results show that the moderate antihyperalgesic effect of pregabalin is mostly seen in dermatomes distant from the pancreas and implies a reduction of central sensitization instead of segmental sensitization. The effect was strongest for superficial tissues, i.e. skin (electric stimulation), and lower for deeper tissues (pressure stimulation). It is suggested that quantitative sensory testing can be of clinical use for monitoring pain treatments in the context of chronic pain.

A further analysis of the experimental endpoints of the randomized controlled trial comparing pregabalin and placebo in chronic pancreatitis were discussed in **chapter 9**. Quantitative sensory testing was used to investigate differences in pain sensitivity and modulation in chronic pancreatitis among responders and non-responders to placebo or pregabalin treatment. Responders were defined as achieving a > 30% pain reduction after three weeks' treatment. Based on their pain response, chronic pancreatitis patients were assigned post-hoc to one of four groups: responders and non-responders to pregabalin (N = 16 and N = 15), or to placebo (N = 12 and N = 17 respectively). Quantitative sensory testing was used to measure change in pain sensitivity before and after treatment, using electric pain detection thresholds in dermatomes C5 (generalized effects) and ventral T10 (segmental effects). Descending endogenous pain modulation was quantified via a conditioned pain modulation (CPM) paradigm. A per protocol analysis was performed on 60 patients. The increase in electric pain detection thresholds in dermatome C5 versus baseline was significant in pregabalin responders ($P < 0.01$). The change in electric pain detection thresholds in C5 was significantly different for pregabalin responders (less hyperalgesia) compared to placebo responders ($P < 0.05$). Similarly to dermatome C5, there was a significant increase in electric pain detection thresholds in dermatome T10, compared to baseline, in pregabalin responders ($P < 0.01$). However, the sizes of the changes in electric pain detection thresholds in the T10 dermatome were similar in the four groups. Conditioned pain modulation versus baseline increased significantly only for pregabalin responders (a more effective response, $P < 0.01$). In contrast, the placebo responders showed a less effective response after three weeks of treatment ($P < 0.05$). The changes in conditioned pain modulation were significantly different between pregabalin responders and placebo responders ($P < 0.001$). This study showed a potent placebo effect on pain relief in chronic pancreatitis patients, although without anti-hyperalgesic effects. In contrast to the placebo group, chronic pancreatitis patients with pain relief on pregabalin did show anti-hyperalgesic effects and increased endogenous inhibitory modulation. These results suggest that the mechanisms underlying analgesic response to placebo and pregabalin are different.

Known causes of pain in chronic pancreatitis are increased intrapancreatic pressure, pancreatic inflammation and pancreatic or extrapancreatic complications. Despite advances

regarding treatments aimed at these causes, chronic pancreatitis pain management remains a major clinical challenge. It is increasingly recognized that changes in central pain processing are also a cause of ongoing chronic pain in chronic pancreatitis. Findings in other visceral pain syndromes (e.g. inflammatory bowel disease and esophagitis) show similar changes in pain processing, and suggest that these and chronic pancreatitis should be managed in a similar fashion. Based on advances in diagnostics and recent improvements in chronic pain management we proposed in **chapter 10** a systematic mechanism-orientated approach to pain management in chronic pancreatitis based on a holistic view of the mechanisms involved. When altered central pain processing is present, conventional pain treatment targeting the nociceptive focus, e.g. opioid analgesia or surgical/endoscopic intervention often fails, even if technically successful. In these cases specific treatment should be instituted, targeting changes in central pain processing such as gabapentinoids, ketamine or tricyclic antidepressants, based on appropriate diagnostic measures. Altered central pain processing can be visualized by quantitative sensory testing, electroencephalography and (functional) magnetic resonance imaging. These diagnostic tools to analyze central pain processing can be useful in defining optimum pain management for chronic pancreatitis and other visceral pain syndromes. Future research should be aimed at a better understanding of changes in central pain processing in chronic pancreatitis and how this is influenced by ongoing nociceptive input and therapies. Furthermore, diagnostic tools aimed at central pain processing should be improved. Such an approach will hopefully help to predict which patients are at risk for developing chronic pain, and which ones will respond positively to an available (given) therapy. This may serve as the basis for achieving personalized medicine.



Appendices

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Het doel van dit proefschrift was om de onderliggende centrale mechanismen van chronische pijn bij chronische pancreatitis te beschrijven en nieuwe inzichten te verkrijgen in deze mechanismen.
De volgende vier doelen werden geformuleerd en zijn besproken in de verschillende hoofdstukken:

1. Het opsporen van veranderingen in de centrale pijnverwerking (centrale sensitisatie) bij chronische pancreatitis
2. Het opsporen van prognostische factoren voor een veranderde centrale pijnverwerking bij chronische pancreatitis
3. Het evalueren van pijnbehandelingen bij chronische pancreatitis en de relatie tussen het succes en veranderde centrale pijnverwerking
4. Het formuleren van een nieuwe, meer holistische benadering van pijn bij chronische pancreatitis, die gebaseerd is op specifieke veranderingen in de centrale pijnverwerking in de individuele patiënt (personalized medicine)

Chronische pancreatitis patiënten met chronische pijn hebben vaak veranderingen in centrale pijnverwerking, die geassocieerd zijn met een abnormale morfologie van het brein. In hoofdstuk 2 berekenden wij met behulp van een 3T magnetische resonantie scanner de corticale dikte van het brein, een maat voor structurele reorganisatie, in hersengebieden die betrokken zijn bij viscerale pijnverwerking. De hersenmorfologie van negentien chronische pancreatitis patiënten met pijn werd geanalyseerd en vergeleken met die van vijftien gezonde individuen. De corticale dikte van de primaire (SI) en secundaire (SII) somatosensorische cortex; prefrontale cortex (PFC); frontale cortex (FC); anterieure (ACC), middelste (MCC), en posterieure (PCC) cingulate cortex; en van de insula werden beoordeeld met behulp van oppervlakte-gebaseerde corticale segmentatie. De occipitale middelste sulcus werd gebruikt als een controle gebied. De pijnscore werd bepaald aan de hand van dagelijkse pijn, gedurende een week. Wij vonden een afname in totale corticale dikte bij chronische pancreatitis patiënten vergeleken met de gezonde individuen ($P < 0.01$). Deze resultaten werden niet beïnvloed door mogelijke verstorende factoren zoals diabetes, alcoholgebruik of behandeling met opioïden (alle $P > 0.05$). Per hersengebied bekeken, was er een significante afname van de corticale dikte in SII ($P < 0.01$), PFC ($P < 0.05$), FC ($P < 0.001$), MCC ($P = 0.001$) en insula ($P < 0.01$), bij chronische pancreatitis patiënten vergeleken met de gezonde individuen. Hersengebieden zonder significante verschillen in corticale dikte tussen beide groepen waren het controlegebied, SI, ACC, en PCC (alle $P > 0.05$). Corticale dikte in de aangedane gebieden was gecorreleerd met de pijnscore ($r = 0.47$, $P < 0.01$). Er werd geconcludeerd dat chronische

pancreatitis patiënten een afname van corticale dikte hebben in hersengebieden die betrokken zijn bij pijnverwerking. Deze veranderingen lijken functionele betekenis te hebben en ondersteunen de huidige literatuur uit basaal en klinisch onderzoek over veranderingen in de centrale pijnverwerking en neurale remodellering. Als gevolg van langdurige, aanhoudende nociceptieve input aan de neuromatrix kan corticale dikte mogelijk dienen als een maat voor dysfunctionele pijnverwerking.

Veranderingen in pijnverwerking in het centrale zenuwstelsel op spinaal en/of supraspinaal niveau door viscerale nociceptieve input spelen een belangrijke rol bij chronische pijn. In **hoofdstuk 3** werden ziektestadium en ziekteprogressie van chronische pancreatitis geïntroduceerd als mogelijke factoren die de uitgebreidheid van veranderingen in centrale pijnverwerking beïnvloeden. Wij verdeelden 60 chronische pancreatitis patiënten op basis van de M-ANNHEIM Severity Index voor chronische pancreatitis in twee subgroepen; 'matig' en 'ernstig' ziektebeloop. Beide groepen werden vergeleken met vijftien gezonde controles. We vergeleken alle drie de groepen met behulp van kwantitatieve sensorische testen voor de detectie en tolerantie van drukpijn en van elektrische pijn, gemeten in zes dermatomen (C5, T4, T10, T10 BACK (dorsaal), L1 en L4). Ook de geconditioneerde pijnmodulatierespons op koude-intolerantie werd gemeten. De resultaten toonden aan dat de chronische pancreatitis patiënten met een 'ernstig' ziektebeloop een lagere drempel hadden voor de detectie van drukpijn ($P < 0.001$), detectie van elektrische pijn ($P < 0.05$) en tolerantie van elektrische pijn ($P < 0.05$) vergeleken met chronische pancreatitis patiënten met een 'matig' ziektebeloop. Ook tussen de 'ernstige' subgroep en gezonde controles werden verschillen gevonden voor de drempel voor detectie van drukpijn ($P < 0.001$), detectie van elektrische pijn ($P < 0.01$) en tolerantie van elektrische pijn ($P < 0.05$) (waarbij de gezonde controles steeds hogere waarden hadden). Er werden geen significante verschillen gevonden in drempels voor tolerantie van drukpijn tussen alle groepen. Ten slotte waren er geen significante verschillen tussen de patiënten met een 'matig' ziektebeloop en gezonde controles voor alle gemeten kwantitatieve sensorische testen. Deze resultaten duiden op variaties in supraspinale centrale sensitisatie ofwel centrale pijnverwerking, die gerelateerd is aan ziekte-ernst: ernstiger ziekte vertoont meer centrale sensitisatie. Descenderende pijnmodulatie, gemeten door de geconditioneerde pijnmodulatierespons was veel sterker (beter) in de gezonde controles vergeleken met alle chronische pancreatitis patiënten ($P < 0.0001$). Dit suggereert dat centrale pijnverwerking niet alleen beïnvloed wordt door ascenderende mechanismes, maar ook door descenderende. Samenvattend, centrale pijnverwerking lijkt beïnvloed te worden door het ziektestadium van de chronische pancreatitis. Hiermee dient rekening gehouden te worden bij de behandeling van pijn bij chronische pancreatitis.

In **hoofdstuk 4** evalueerden wij de relatie tussen pijnverwerking en pijn na chirurgische decompressie van de ductus pancreaticus en/of partiële pancreasresectie bij chronische pancreatitis patiënten. Kwantitatieve sensorische testen werden gebruikt om in 48 chronische pancreatitis patiënten drempels voor de detectie en tolerantie van elektrische pijn te meten in twee dermatomen die op afstand liggen van het pancreas dermatoom (C5 en L4). Descenderende pijnmodulatie werd gemeten door de geconditioneerde pijnmodulatierespons. Chronische pancreatitis patiënten werden onderverdeeld in twee subgroepen op basis van hun pijn na pancreaschirurgie: 'slechte pijnuitkomst' (score gemeten op een visuele analoge schaal (VAS) van meer dan 30) en 'goede pijnuitkomst' (VAS score van 30 of minder). Chronische pancreatitis patiënten werden vergeleken met vijftien gezonde controles. De gehele groep chronische pancreatitis patiënten had een lagere drempel voor de detectie en tolerantie van elektrische pijn, evenals een lagere geconditioneerde pijnmodulatierespons in vergelijking met gezonde controles ($P < 0.05$). Patiënten met een 'slechte pijnuitkomst' na de ingreep hadden lagere elektrische pijn detectie drempels dan patiënten met een 'goede pijnuitkomst' ($P < 0.01$). Er was een negatieve correlatie tussen de VAS score en de drempels voor detectie van elektrische pijn ($rs = -0.45$, $P < 0.05$), tolerantie van elektrische pijn ($rs = -0.46$, < 0.05) en geconditioneerde pijnmodulatierespons ($rs = -0.43$, $P < 0.01$) bij chronische pancreatitis patiënten. Concluderend vertonen chronische pancreatitis patiënten na pijnverlichtende pancreaschirurgie een veranderde pijnverwerking. Chronische pancreatitis patiënten met een 'slechte pijnuitkomst' na de operatie toonden meer centrale sensitisatie en meer pronociceptive descenderende pijnmodulatie dan chronische pancreatitis patiënten met een 'goede pijnuitkomst' na de operatie. Deze resultaten suggereren dat de gevonden veranderingen relatief onafhankelijk van de perifere nociceptieve input zijn geworden. De waargenomen verschillen moeten worden meegenomen bij het behandelen van aanhoudende pijn na pijnverlichtende pancreaschirurgie bij chronische pancreatitis, en moet onder controle zijn voordat een nieuwe chirurgische ingreep wordt overwogen.

In vervolg op de studies uit hoofdstuk 3 en 4 werden in **hoofdstuk 5** veranderingen in pijnverwerking bij chronische pancreatitis verder onderzocht. Mogelijk is er centrale sensitisatie - onafhankelijk van perifere nociceptieve input - aanwezig bij chronische pancreatitis patiënten die geen baat hebben gehad van denervatie procedures van het pancreas. In deze gevallen is de oorzaak van de pijn niet de nociceptieve input vanuit het pancreas, maar een gevolg van aanhoudende autonome veranderingen in het centrale zenuwstelsel. Wij onderzochten of bilaterale thoracoscopische splanchnicusdenervatie, uitgevoerd om nociceptieve input te verminderen bij chronische pancreatitis patiënten, de centrale pijnverwerking beïnvloedt. Zeventien chronische pancreatitis patiënten werden preoperatief en zes weken na bilaterale thoracoscopische splanchnicusdenervatie onderzocht. Drempels voor drukpijn werden gemeten met

behulp van kwantitatieve sensorische testen voor en na splanchnicusdenervatie in een dermatoom ver van het pancreas gelegen (C5) en in het pancreas dermatoom (T10), als afspiegeling van respectievelijk supraspinale en spinale centrale sensitisatie. Chronische pancreatitis patiënten werden verdeeld in twee groepen op basis van hun veranderingen in pijndrempels: 'hypoalgetische' patiënten hadden een stijging van de drempels na interventie en 'hyperalgetische' patiënten hadden een afname of geen verandering van de drempels na interventie. Deze onderverdeling werd zowel gemaakt voor het pancreas dermatoom (dorsaal T10), als voor het dermatoom ver van het pancreas (C5). Postoperatieve pijnscores op een numerieke schaal (NRS) werden gecorreleerd aan de veranderingen in pijndrempels. Na splanchnicusdenervatie vertoonden tien patiënten een toename in drempels voor drukpijn in C5 (hypoalgetisch), zeven patiënten hadden ongewijzigde of lagere drempels voor drukpijn (hyperalgetisch). De preoperatieve pijnscore (NRS) was vergelijkbaar tussen de groepen (mediaan 4 vs. 5). Na splanchnicusdenervatie was in de 'hypoalgetische' groep de pijnscore lager (mediaan 1 vs. 6, $P < 0.01$) en de verandering in pijnscore groter (mediaan -2 vs. 0, $P < 0.01$). De pijnscore en drempel voor drukpijn in dermatoom C5 lieten een statistisch significante negatieve correlatie zien ($rs = 0.53$, $P < 0.05$); dit was niet het geval voor drempels voor drukpijn in het pancreasdermatoom. We vonden dat een toename van drempels voor drukpijn in een dermatoom ver van het pancreas dermatoom gelegen (C5), als afspiegeling van supraspinale sensitisatie, was geassocieerd met een significante afname in postoperatieve pijnscore na bilaterale thoracoscopische splanchnicusdenervatie. Dit was niet het geval voor het pancreas dermatoom (T10), als afspiegeling van meer segmentale spinale pijnverwerking. Deze resultaten suggereren dat een subgroep van chronische pancreatitis patiënten met chronische pijn veranderingen heeft in pijnverwerking die mogelijk onafhankelijk zijn van perifere nociceptieve input. Dit resulteert in persisterende pijn ondanks bilaterale thoracoscopische splanchnicusdenervatie. Indien bevestigd in toekomstige studies, geven deze resultaten het belang aan van sensorische testen voor de indicatie en toepassing van pijnbehandelingen. Daarbij kunnen deze testen preoperatief van prognostische waarde zijn voor wie baat heeft bij een interventie en postoperatief voor het meten van het effect van de interventie.

Centrale sensitisatie en hyperalgesie, belangrijke processen bij chronische pijn, zijn geassocieerd met N-methyl-D-aspartaat (NMDA) receptoractivatie. In **hoofdstuk 6** is het effect van S-ketamine (NMDA receptorantagonist) en placebo beschreven op gegeneraliseerde hyperalgesie en pijn bij chronische pancreatitis patiënten. Wij voerden een geblindeerde cross-over studie uit, waarin tien chronische pancreatitis patiënten gerandomiseerd werden voor ofwel een drie uur durende infusie van S-ketamine (2 mcg/kg/min) ofwel placebo. Klinische pijn werd beoordeeld middels een VAS score en de Nederlandse vertaling van de McGill Pain Questionnaire (sf-MPV-DLV). Drempels

voor drukpijn werden gemeten door middel van kwantitatieve sensorische testen in de dermatomen C5, T4, T10 BACK (dorsaal), L1 en L4. De som van de drempels voor drukpijn werd berekend vóór infusie, direct na het stoppen van de infusie en één uur na de infusie. Gedurende de infusie van S-ketamine en placebo rapporteerden patiënten weinig bijwerkingen. Wanneer er sprake was van een bijwerking dan was deze mild en gaf deze geen reden tot staken van de infusie. De mediane VAS score vóór infusie was 29 mm in rust en 32 mm tijdens activiteit. Patiënten in de S-ketamine groep vertoonden een significante toename van de som van drempels voor drukpijn direct na het stoppen van de infusie, vergeleken met waardes vóór infusie ($P < 0.05$) en vergeleken met de placebogroep ($P < 0.01$). De significante toename van de drempels voor drukpijn in de S-ketamine groep was kortdurend, aangezien de som van drempels voor drukpijn één uur na infusie vergelijkbaar was met pre-infusie waardes en met die van de placebo groep. Er werden geen significante verschillen waargenomen in VAS score en sf-MPV-DLV score gedurende de studie. Deze studie toonde aan dat bij chronische pancreatitis patiënten met pijn, S-ketamine direct na infusie effectiever is dan placebo in het verhogen van drempels voor drukpijn. Deze resultaten bevestigen het acute anti-hyperalgetische effect van S-ketamine. Ondanks het positieve korte termijn effect van S-ketamine op de pijndrempels was het effect na het stoppen van de infusie snel weer verdwenen. Veel is nog onbekend over de optimale dosering, duur en route van toediening van S-ketamine, wat het definiëren van een optimaal behandelschema moeilijk maakt. Wanneer deze onderwerpen beter onderzocht zijn is een langer aanhoudend effect van S-ketamine mogelijk te bewerkstelligen.

Medicatie zoals pregabaline wordt gebruikt om patiënten met neuropathische pijn te behandelen. Basaal wetenschappelijk onderzoek en humane studies hebben aangetoond dat sommige chronische pancreatitis patiënten een abnormale pijnverwerking hebben, die gelijkenissen vertoont met die van patiënten met neuropathische pijn. In **hoofdstuk 7** onderzochten we het effect van pregabaline als adjuvante pijnstiller op de pijn bij chronische pancreatitis patiënten. Vierenzestig patiënten werden gerandomiseerd in deze dubbelblinde, placebo-gecontroleerde studie. Patiënten kregen gedurende drie achtereenvolgende weken opklimmende doses van pregabaline of placebo. Het primaire eindpunt was klinische pijn, gemeten op basis van de VAS score, gedocumenteerd in een pijndagboek. Secundaire eindpunten waren de 'globale indruk van verandering in pijn' (PGIC score), veranderingen in fysieke en functionele scores, het karakter van de pijn, kwaliteit van leven en tolerantie van de studiemedicatie. Pregabaline gaf een effectievere pijnreductie dan placebo na drie weken van behandeling (36% vs. 24%, $P < 0.05$). Het percentage patiënten met een sterk tot een zeer sterk verbeterde gezondheidstoestand aan het einde van de studie was hoger in de pregabalinegroep dan in de controlegroep (PGIC score 44% vs. 21%, $P < 0.05$). Veranderingen in de fysieke en functionele scores,

karakter van de pijn, kwaliteit van leven en het aantal bijwerkingen (meestal mild tot matig) waren vergelijkbaar tussen beide groepen. De maximale dosering van studiemedicatie werd door 61% van de patiënten in de pregabalinegroep verdragen, tegenover 90% in de placebogroep. Therapietrouw was hoog in beide groepen (> 90%). Deze studie toonde de werkzaamheid en tolerantie van pregabaline aan als adjuvante pijnstiller in de behandeling van pijn bij chronische pancreatitis patiënten. Een dosering van pregabaline tussen de 150 mg en 300 mg tweemaal daags resulteerde in een klinisch significante vermindering van de pijn.

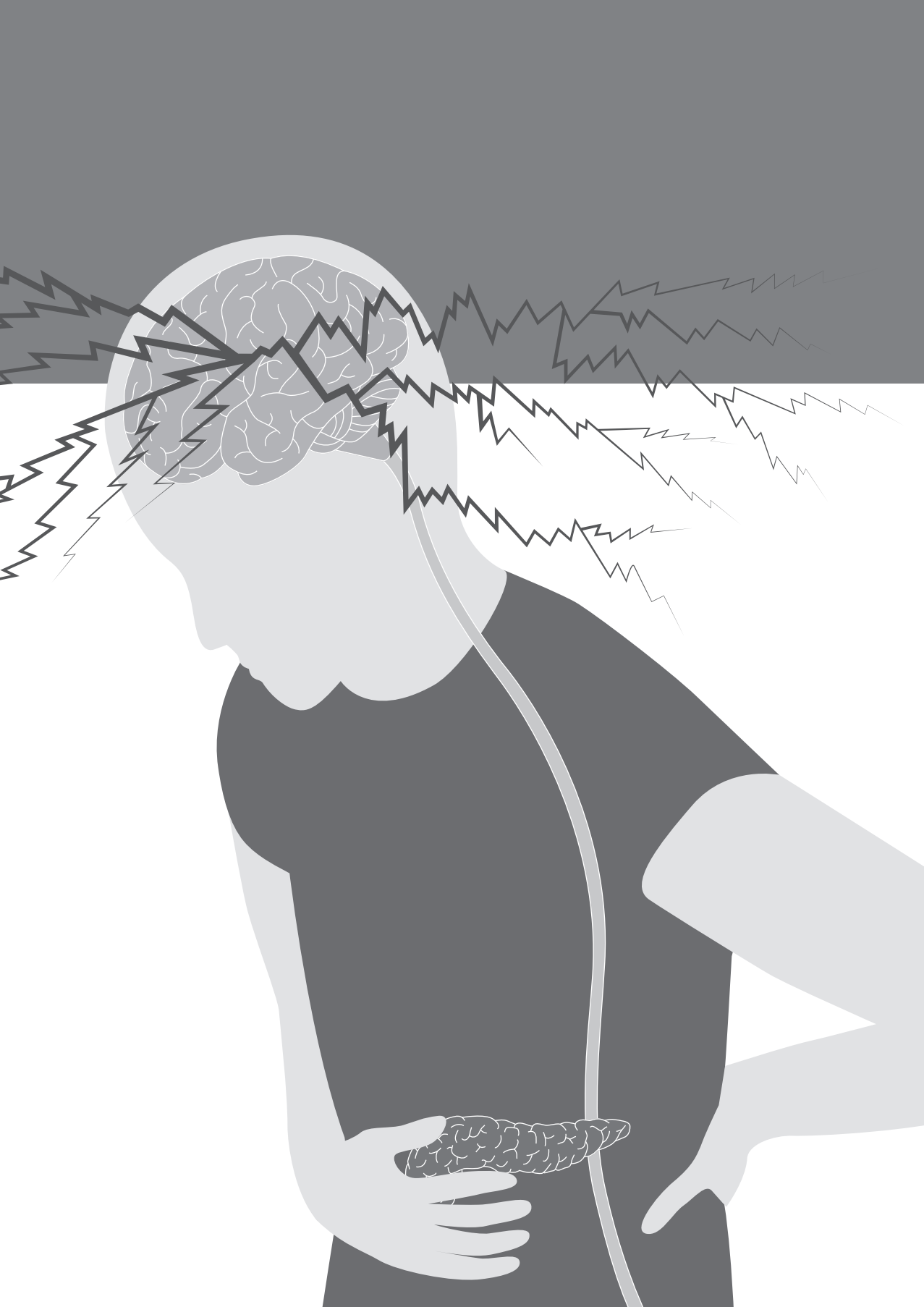
In **hoofdstuk 8** werden de experimentele eindpunten beschreven van de in hoofdstuk 7 beschreven studie. Het doel van de studie was om het effect van pregabaline op pijnverwerking te evalueren bij chronische pancreatitis patiënten door middel van kwantitatieve sensorische testen. Drempels voor elektrische pijn en drukpijn werden gemeten in zes verschillende dermatomen (C5, T4, T10, L1, L4 en T10 BACK (dorsaal)). Descenderende pijnmodulatie werd gekwantificeerd door middel van de geconditioneerde pijnmodulatierespons. De belangrijkste uitkomstmaat was de verandering in de som van alle drempels voor elektrische pijn en drukpijn uit alle dermatomen na drie weken behandeling met de studiemedicatie ten opzichte van de baselinewaardes in beide studiegroepen. Alle 64 gerandomiseerde patiënten werden geanalyseerd. Veranderingen in de som van drempels voor elektrische pijn en drukpijn waren vergelijkbaar tussen de pregabaline en de placebogroep na drie weken behandeling met de studiemedicatie. Voor de afzonderlijke dermatomen was de toename in pijndrempels (na de behandeling) significant groter in de pregabalinegroep dan in de placebogroep voor de volgende stimuli: elektrische pijn in dermatoom C5 ($P < 0.01$), tolerantiedrempel van elektrische pijn in dermatomen C5 ($P < 0.05$) en L1 ($P = 0.05$), en tolerantie van drukpijn in dermatoom T4 ($P < 0.01$). Er werden geen verschillen waargenomen tussen pregabaline en placebo met betrekking tot de geconditioneerde pijnmodulatierespons. Deze resultaten tonen een gematigd anti-hyperalgetisch effect van pregabaline, met name in dermatomen ver van het pancreas gelegen, en duiden op vermindering van centrale sensitisatie in plaats van segmentale sensitisatie. Dit effect was sterker bij oppervlakkige weefsels zoals de huid (elektrische stimulatie) dan in dieper gelegen weefsels (drukstimulatie). Deze bevindingen suggereren dat kwantitatieve sensorische testen van klinisch nut kunnen zijn voor het monitoren van pijnbehandeling in de context van chronische pijn en het vinden van prognostische factoren die het klinisch succes beïnvloeden.

Een nadere analyse van de experimentele eindpunten uit de pregabaline studie werd besproken in **hoofdstuk 9**. Kwantitatieve sensorische testen werden gebruikt om verschillen in gevoeligheid voor pijnprikkels en pijnmodulatie tussen responders en non-responders op een behandeling met placebo of pregabaline bij chronische pancreatitis patiënten te onderzoeken. Responders werden gedefinieerd als > 30% pijnreductie na

de behandeling van drie weken. Op basis van het verschil in pijn na studiebehandeling werden de chronische pancreatitis patiënten verdeeld over vier groepen: responders en nonresponders op pregabaline (N = 16 resp. N = 15) en responders en nonresponders op placebo (N = 12 resp. N = 17). Kwantitatieve sensorische testen werden gebruikt om veranderingen in de gevoeligheid voor pijnprikkels voor en na de behandeling te meten, gebruikmakend van drempels voor de detectie van elektrische pijn in dermatoom C5 (gegeneraliseerde effecten) en ventrale T10 (segmentale effecten). Descenderende endogene pijnmodulatie werd gekwantificeerd door middel van de geconditioneerde pijnmodulatierespons. Een per protocol analyse werd uitgevoerd op 60 patiënten. De toename van drempels voor de detectie van elektrische pijn in dermatoom C5 ten opzichte van de uitgangswaarde was statistisch significant in de pregabalineresponders ($P < 0.01$). De verandering in drempels voor de detectie van elektrische pijn in C5 was significant verschillend (minder hyperalgesie) voor pregabalineresponders in vergelijking met placeboresponders ($P < 0.05$). Een statistisch significante toename in drempels voor de detectie van elektrische pijn vergeleken met uitgangswaardes werd gevonden in pregabalineresponders in dermatoom T10 ($P < 0.01$) en in dermatoom C5 ($P < 0.01$). De grootte van de veranderingen in drempels voor de detectie van elektrische pijn in het T10 dermatoom was vergelijkbaar tussen de vier groepen. Geconditioneerde pijnmodulatierespons versus uitgangswaardes was alleen statistisch significant hoger in de pregabalineresponders (een effectievere respons, $P < 0.01$). De placeboresponders lieten daarentegen een minder effectieve respons na drie weken behandeling zien ($P < 0.05$). De veranderingen in de geconditioneerde pijnmodulatie waren significant verschillend tussen pregabalineresponders en placeboresponders ($P < 0.001$). Deze studie toonde een sterk placebo-effect op pijn bij chronische pancreatitis patiënten, echter zonder antihyperalgetische effecten. In tegenstelling tot de placebogroep lieten chronische pancreatitis patiënten met pijnvermindering op pregabaline antihyperalgetische effecten en een versterkte endogene pijnmodulatie zien. Deze resultaten suggereren dat de onderliggende mechanismes die een analgetische respons op placebo en op pregabaline teweeg brengen, verschillend zijn.

Bekende oorzaken van pijn bij chronische pancreatitis zijn: verhoogde intrapancreatische druk, opvlamming van de pancreatitis en (extra)pancreatische complicaties. Ondanks de geboekte vooruitgang in de behandeling van deze oorzaken, blijft de behandeling van pijn bij chronische pancreatitis een uitdaging. Veranderingen in centrale pijnverwerking wordt steeds meer erkend als oorzaak van aanhoudende intense pijn bij chronische pancreatitis. Vergelijkbare veranderingen in centrale pijnverwerking worden ook in andere viscerale pijn syndromen, zoals inflammatoire darmziekten en oesofagitis, gevonden en suggereert dat deze syndromen een vergelijkbare behandeling van pijn vergen. In **hoofdstuk 10** stelden we op basis van bekende pijnmechanismen en

recente ontwikkelingen, met betrekking tot de diagnostiek en behandeling van pijn bij chronische pancreatitis, een systematische benadering van pijn voor bij chronische pancreatitis. Alvorens behandeling te starten, dient goede diagnostiek verricht te worden naar veranderingen in centrale pijnverwerking. Deze veranderingen kunnen worden vastgesteld door middel van kwantitatieve sensorische testen, elektro-encefalografie en (functionele) beeldvorming door middel van magnetische resonantie. Daarbij kunnen deze diagnostische hulpmiddelen nuttig zijn om centrale pijnverwerking te analyseren en te helpen bij het bepalen van de optimale pijnbestrijding voor chronische pancreatitis en andere viscerale pijnsyndromen. In het geval dat conventionele pijnbehandeling (opioïden, chirurgie en/of endoscopie) gericht op de nociceptieve bron faalt, is vaak de centrale pijnverwerking veranderd. In deze gevallen dient een specifieke behandeling gericht op centrale pijnverwerking te worden ingesteld, bijvoorbeeld met gabapentinoïden, ketamine of tricyclische antidepressiva. Toekomstig onderzoek moet gericht zijn op een beter begrip van veranderingen in de centrale pijnverwerking en de diagnostiek hiervan en hoe deze beïnvloed wordt door onze interventies. Daarbij zal de invloed van aanhoudende (chronische) nociceptieve input hierop uitgediept moeten worden om tot een betere behandeling te komen. Een dergelijke aanpak zal helpen om te voorspellen welke patiënten een verhoogd risico hebben op het ontwikkelen van chronische pijn, en welke positief zullen reageren op een bepaalde therapie, zodat een individueel behandelplan bereikt kan worden.



Appendices

Dankwoord

DANKWOORD

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Nicolien Scheepers, rasoptimist met onuitputtelijke energie. Je nam de PONCHO coördinatie van mij over en zette de APEC trial ondertussen op. Met verve coördineer je de Werkgroep en ben je uitgegroeid tot een kritisch onderzoeker die overloopt van ideeën. Succes met het afronden van APEC en met de start van je opleiding tot MDL-arts. Ik hoop in de toekomst nog veel van je aanwezigheid te mogen genieten.

David Da Costa, je nam PONCHO van mij over en we hebben ondertussen de studie mooi weg kunnen zetten. De studie is in goede handen bij je gekomen en zal zeker leiden tot een mooi proefschrift. Onze samenwerking is nog lang niet klaar en ik kijk uit naar de vervolgstudies van PONCHO. Succes met je plannen voor na je promotie, ik ben ervan overtuigd dat je een goede plek zult vinden.

Janneke van Grinsven, Bob Hollemans, Xavier Smeets, Noortje Hallensleben, jullie kwamen als nieuwe arts-onderzoekers bij de Werkgroep toen ik al vertrokken was. Het is mooi om te zien dat door jullie enthousiasme nieuwe energie in de groep is gekomen en jullie anderen nu op sleeptouw nemen. Succes met jullie studies en ik zie uit naar jullie proefschriften.

Vera Zeguers, Hellen van Wezel, Hetty van der Eng en Anneke Roeterdink. Jullie waren de drijvende kracht achter het datacentrum en de trials. Geen enkele arts, secretaresse of verpleegkundige ontkwam aan jullie vasthoudendheid totdat de patiënt was geïncludeerd of de gegevens waren verkregen. Dank voor jullie goede werk, adviezen en gezelligheid.

Marjan de Vries en Tjarda Tromp, het kan geen toeval zijn dat jullie weer een kamer delen. Ondertussen zijn jullie onmisbaar binnen de afdeling en kan ik, net zoals jaren geleden, nog steeds binnen lopen voor een goed gesprek of een lach. Het is jammer dat er geen derde werkplek is op jullie kamer.

Collega promovendi en andere oud kamergenoten. Onderzoek doen kan je overal, maar op de oude afdeling was het altijd erg goed toeven. Het was in de winter flink stoken en in de zomer soms onhoudbaar, maar de sfeer was altijd goed. Absolute hoogtepunten waren het met zijn allen organiseren van de Chirurgencup en de skiweekenden met de afdeling. Excuus voor mijn soms drukke aanwezigheid en dank voor de mooie tijd.

Dr. Rosman en dr. Verhoeven, beste Camiel en Bas, jullie hebben mij altijd aangemoedigd om mijn opleiding zelf in te vullen en elke keer weer op zoek te gaan naar nieuwe uitdagingen. Dank voor het ondersteunen van mijn onderzoek en de persoonlijke begeleiding gedurende mijn opleiding.

Beste chirurgen in het Canisius-Wilhelmina Ziekenhuis. Bij binnenkomst in jullie ziekenhuis was ik onervaren en groen als gras. Dankzij jullie vertrouwen en geduld heb ik een goede basis in de chirurgie gekregen. Sinds dag één in het CWZ was ik verkocht aan ons vak. Sindsdien is mijn enthousiasme hiervoor alleen maar gegroeid en dit is grotendeels jullie verdienste. Ik zie ernaar uit om mijn opleiding verder te mogen vervolgen bij jullie. Dank voor de leerzame tijd en mooie momenten tijdens en na het werk.

Beste chirurgen in het Radboudumc. Dank voor de warme ontvangst die ik wederom mocht krijgen. De sfeer op de afdeling is goed en er heerst een prettig opleidingsklimaat. Naast het opereren geven jullie ons assistenten de mogelijkheid om ons ook op andere vlakken te ontwikkelen, en het onderzoek bloeit als nooit tevoren. Dank voor de belangstelling voor en de ondersteuning van mijn onderzoek.

Collega's en oud-collega chirurgen in opleiding. Als onderzoeker en AIOS tegelijk heb je een soort van gespleten persoonlijkheid. Zonder jullie steun in de kliniek had ik deze twee paden niet tegelijk kunnen bewandelen. Samen maken we de sfeer en die is goed. Hopelijk blijven we in toekomst genoeg tijd houden voor nog veel leuks op en na het werk.

Mannen van de culiclub, als jongste van het gezelschap voel ik mij wel het nakomertje tussen de gepromoveerden. De weekenden naar de Elzas of het hoge Noorden hebben we inmiddels verruild voor koken dicht bij huis. Ondertussen is er een flinke aanwas en komen we niet meer met zijn zessen samen maar met twintig plus. Dank voor de toffe weekenden en de mooie tijd samen.

Mannen van de culiclub (op zondag), ik hoop dat we in de toekomst met zo'n diverse groep samen kunnen blijven komen in Lent. Dank voor de prettige afwisseling buiten het medische vak.

Mannen van Ferus Ebrius, wat hebben we door de jaren heen toch veel samen meegemaakt en veel lol gehad. Van studenten in oranje tuinbroek naar, voor sommigen, een wit pak met klompen. Hechte vriendschappen heb ik overgehouden aan deze tijd en ik kan mij geen betere studententijd voorstellen dan ik samen met jullie heb gehad.

Beste Stijn, Bram, Martijn, Ruben, Jimmie en Theo, we hebben een mooie club met zijn allen. Straks is mijn onderzoek geen excuus meer en ik kijk uit naar al het moois wat we nog met zijn allen gaan doen.

Beste paranimfen, wat is het fijn dat jullie mij bij willen staan op dit unieke moment. Stijn, straks staan we net zoals vroeger in rokkostuum, alleen nu zonder blackjack tafel en met een *wit* rokhemd. Caesar, we hebben al zo veel samen mogen delen, prachtig dat we dit aan het rijtje kunnen toevoegen.

Beste familie, kennissen en vrienden van thuis. Wat is het soms jammer dat Zeeland toch een flink stuk reizen is vanuit Nijmegen. Desalniettemin voelt de rit naar de kust nog steeds als thuiskomen. Dank voor alle support in voor- en tegenspoed. Dit proefschrift is misschien een Nijmeegse aangelegenheid, maar de basis voor dit alles lag bij jullie.

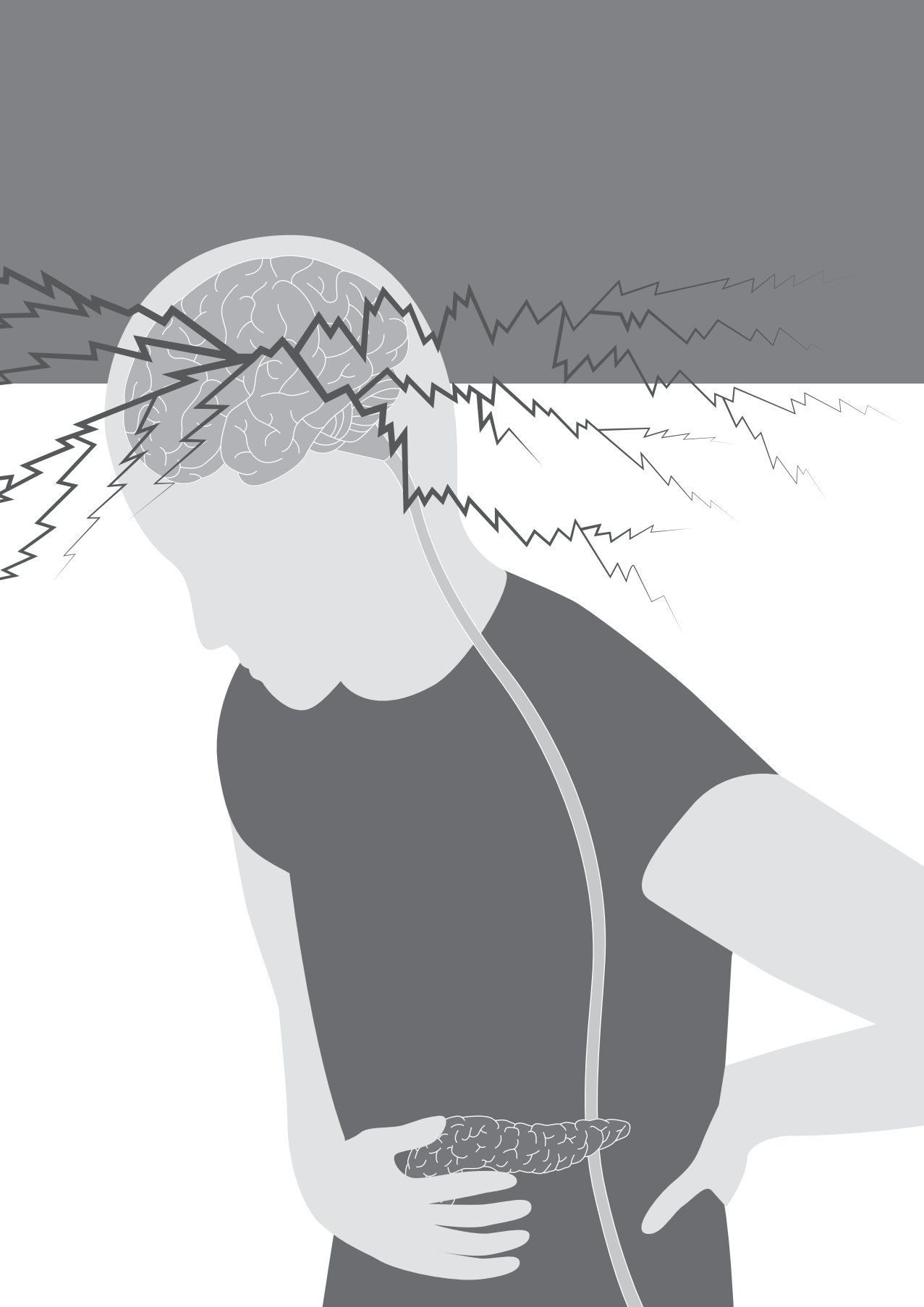
Schoonfamilie Luijks, sinds ik Hilde leerde kennen staat jullie deur altijd wagenwijd open, met daarachter immer gezelligheid. Ondanks dat dit proefschrift en andere verplichtingen geregeld voor mijn afwezigheid zorgden, bleven jullie dit steunen en kwamen er opbeurende woorden als dit nodig was. Met trots kijken jullie al uit naar onze beide promoties en ik ben blij dat we dat met zijn allen kunnen vieren. Dank voor alles.

Beste opa, u wordt 98 en op uw hoge leeftijd staat u nog steeds positief in het leven, met veel interesse in de mensen om u heen. Het is fijn om te zien hoe enthousiast u bent als uw geliefde (achter)kleinkinderen u bezoeken. Hopelijk bent u in staat om de verdediging bij te wonen en kunnen we de komende tijd van u blijven genieten.

Eveline, Caesar en Jules, wat zijn jullie met zijn drieën een geweldig stel. De 2e telg van jullie gezin is op komst en ik kijk erg uit naar zijn komst. We wonen jammer genoeg niet bij elkaar om de hoek, maar via facetime kunnen we tegenwoordig goed contact houden. Ik ben trots op wat jullie hebben bereikt en soms ook wat jaloers op jullie mooie stekkie in Willemstad. Dank voor jullie immer luisterend oor en oprechte interesse.

Pa en ma, jaren geleden hadden we het denk ik nooit verwacht: een promotie in de medische wetenschappen. Dank voor alle vrijheid die jullie mij hebben gegeven in het maken van eigen keuzes. Of het nu de ad hoc switch van de TU naar de RU, of een verre reis ‘voor de studie’ was, jullie steunden me altijd en stonden steeds voor mij klaar. Dit proefschrift was er niet geweest zonder jullie adviezen, liefde en zorg.

Lieve Hilde, ik bewonder je om wie je bent en om wat je in mij boven haalt. Zonder jouw luisterend oor en peptalks was dit alles er niet geweest. Wat heb je ongekend hard gewerkt aan je eigen proefschrift de afgelopen tijd. Met als resultaat dat we nagenoeg tegelijk kunnen promoveren en dit samen kunnen gaan vieren. Geweldig! Samen met Joost gaan we een mooie tijd tegemoet. Jij bent de liefde van mijn leven!



Appendices

Curriculum vitae

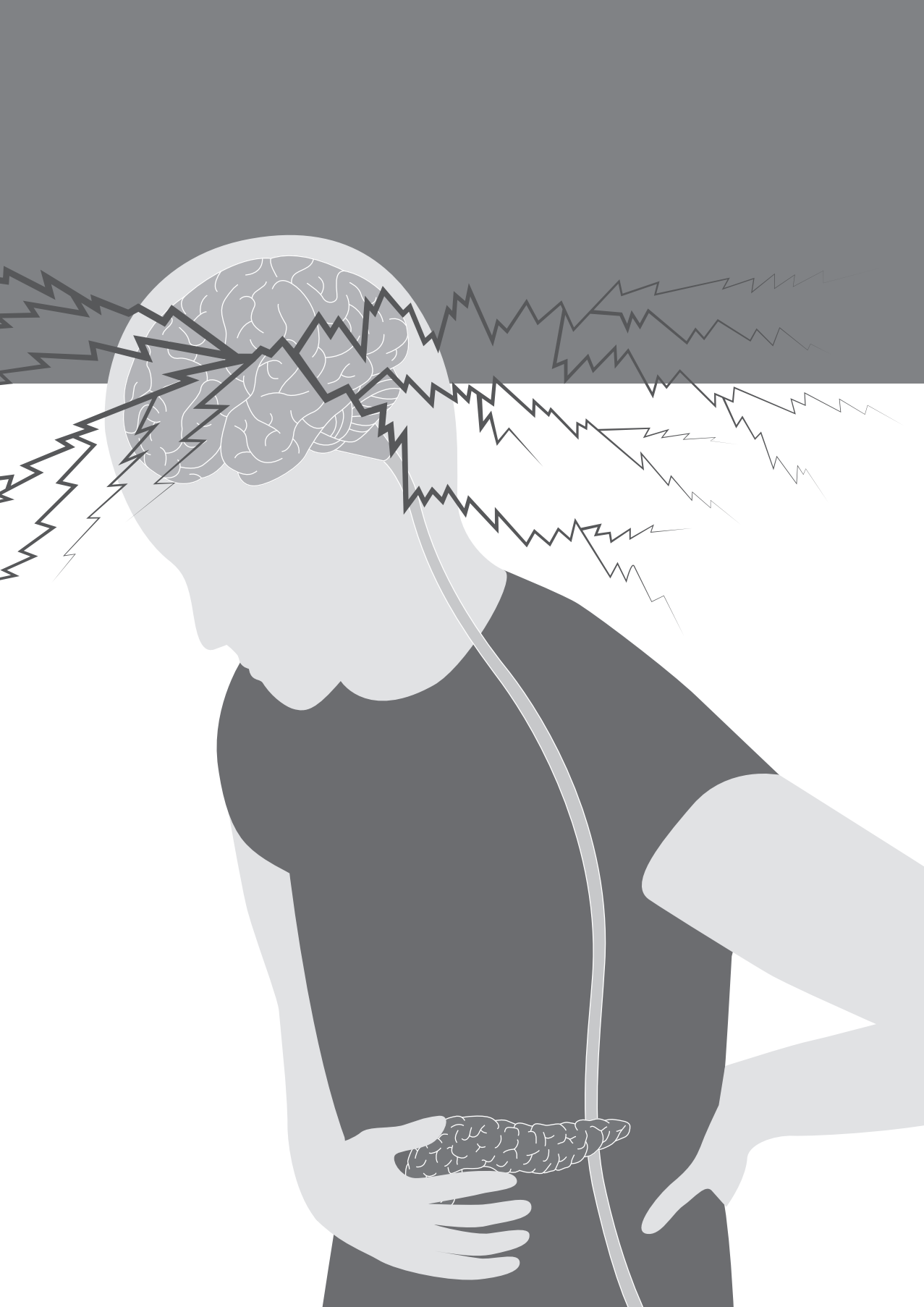
CURRICULUM VITAE

Stefan Bouwense was born on the 12th of May in 1984. He spent his childhood in Kortgene, a small town in the province of Zeeland, the Netherlands. After graduating from the Goese Lyceum in Goes, he studied medicine from 2002 – 2010 at the Radboud University Nijmegen. Next to his medicine studies, he was active as treasurer for the Medical Students' Association Nijmegen (2004 – 2005), worked as a student-assistant for the departments of Pathology and Internal Medicine of the Radboud university medical center, and was a member of the fraternity M.H.D. Ferus Ebrius. In 2007 he went to Brisbane, Australia, for a research internship, where he joined the orthopedic research group of prof. R. Crawford at the Queensland University of Technology. During his clinical internships he participated in research at the department of Radiology and started with research in chronic pancreatitis under supervision of prof. dr. H. van Goor and dr. O.H.G. Wilder-Smith at the department of Surgery.

After graduation in 2010, Stefan continued his research in chronic pancreatitis. These research activities were the basis for his PhD-thesis. He also joined the research group of prof. dr. H.G. Gooszen in 2010 and started research in acute pancreatitis for the Dutch Pancreatitis Study Group. His main task was coordinating a randomized controlled trial: the PONCHO trial (timing of cholecystectomy after mild biliary pancreatitis) under supervision of dr. D. Boerma, dr. B. Van Ramshorst and dr. M.G.H. Besselink.

In July 2012 he started his residency in surgery at the Canisius-Wilhelmina Hospital in Nijmegen (dr. C. Rosman and dr. B. Boll), which was continued at the Radboud university medical center (dr. B.H. Verhoeven and prof. dr. C.J.H.M van Laarhoven) in 2015.

Stefan Bouwense is the (co-)author of over 25 peer-reviewed articles and book chapters. He lives together with Hilde Luijks and their son Joost in Nijmegen.



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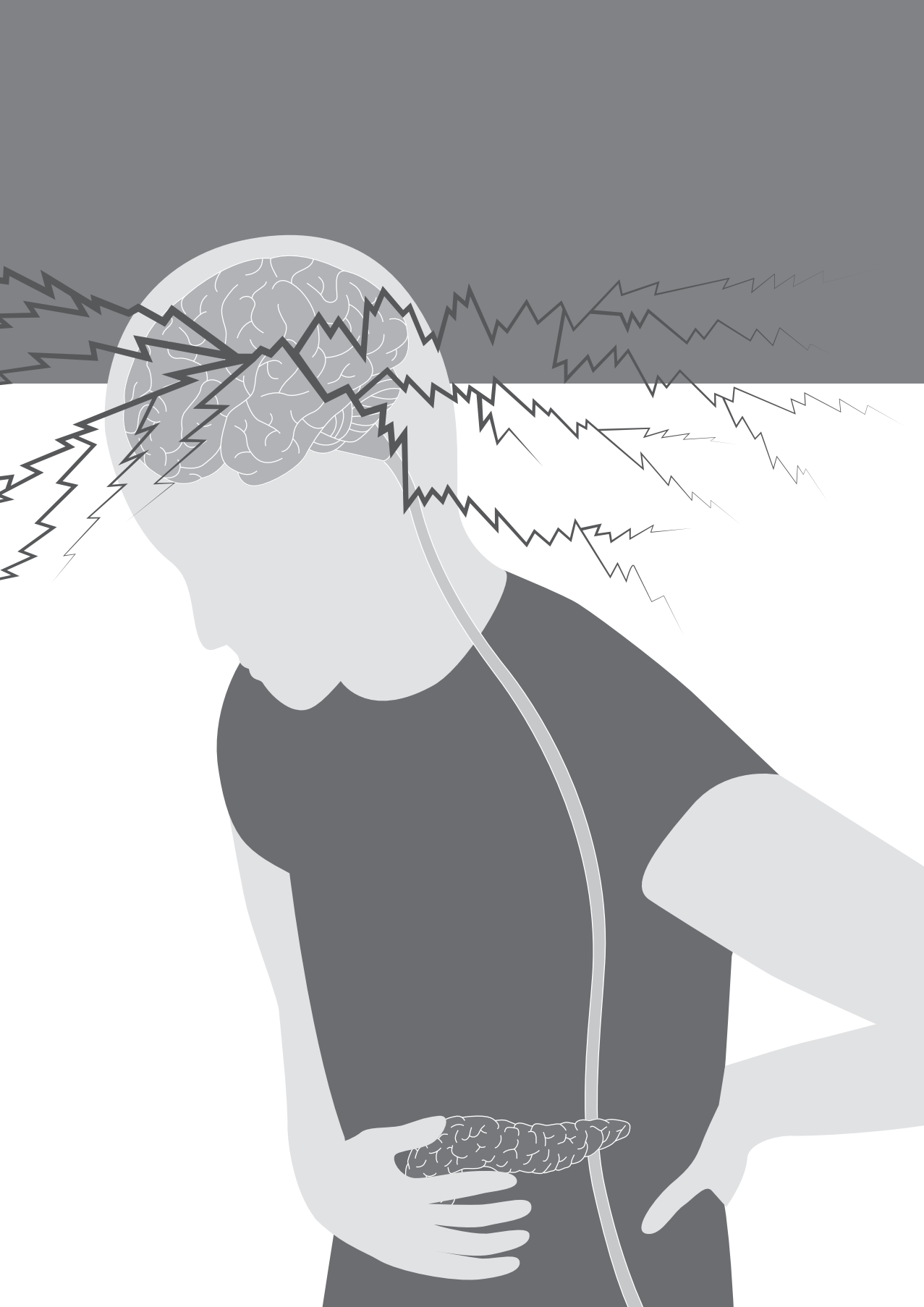
* authors contributed equally



Appendices

RIMLS PhD portfolio

RIMLS PHD PORTFOLIO

Institute for Molecular Life Sciences
Radboudumc

Name PhD student: *S.A.W. Bouwense*
Department: *Surgery*
Research School: *Nijmegen Centre for Molecular Life Sciences*

PhD period: *sept 2010 – dec 2014*
Promotor(s): *prof. dr. H. van Goor & prof. dr. H.G. Gooszen*
Co-promotor(s): *dr. O.H.G. Wilder-Smith DSc*

	Year(s)	ECTS
TRAINING ACTIVITIES		
a) Courses & Workshops		
- Randomized clinical trials, University of Oxford, Oxford	2010	1.75
- Talent classes: writing articles & presenting & networking, NWO, Den Haag	2010	0.6
- BROK cursus & medical writing, PAO Heyendael, Nijmegen	2010	1.75
b) Seminars & lectures		
- Dutch Highlights at IHPBA, Zeist	2010	0.25
- Pancreasdag, Utrecht	2012	0.25
- Pancreasdag, Utrecht	2014	0.25
c) (Inter)national Symposia & congresses		
- Najaarsvergadering NVvH, Ede (oral presentation)	2010	0.5
- Voorjaarscongres NVGE, Veldhoven (oral presentation)	2011	0.75
- Digestive Disease Week, Chicago (oral presentation)	2011	1.75
- Pancreasclub, Chicago	2011	0.25
- European Pancreatic Club, Magdeburg (poster presentation)	2011	1.5
- European Federation of IASP Chapters - PAIN IN EUROPE VII, Hamburg (poster presentation)	2011	1.5
- Najaarsdag NVGE, Ede	2011	0.25
- 19th United European Gastroenterology Week, Stockholm (2x poster presentation)	2011	2.25
- Najaarsvergadering NVvH, Ede	2011	0.25
- 6th World Congress of the World Institute of Pain, Miami (4x poster presentation)	2012	2.75
- Alpine Liver and Pancreatic Surgery meeting, Madonna di Campiglio (oral presentation)	2012	1.75
- Chirurgendagen, Veldhoven	2012	0.5
- Digestive Disease Week, San Diego	2012	1
- Pancreasclub, San Diego	2012	0.25
- World Congress of Pain clinicians, Granada (oral and poster presentation)	2012	2.0
- American Pancreatic Association annual meeting, Miami (oral presentation)	2012	1.5
- Danish Pancreatitis Club, Copenhagen (oral presentation)	2012	0.75
- Najaarsvergadering NVvH, Veldhoven	2012	0.25
- Chirurgendagen, Veldhoven	2013	0.5
- Najaarsvergadering NVvH, Veldhoven	2013	0.25
- Digestive Disease Week, Chicago (oral presentation)	2014	1.5
- Chirurgendagen, Veldhoven	2014	0.5
- Najaarsdag NVGE, Veldhoven (oral presentation)	2014	0.75
- Najaarsvergadering NVvH, Utrecht (oral presentation)	2014	0.5
d) Other		
- Reviewing scientific publications for different journals	2012-2015	0.7
- Reviewing abstracts for Digestive Disease Week 2015	2014	0.5
- Organization and participation in meetings of the Dutch Pancreatitis Study Group	2010-2012	1.5
TEACHING ACTIVITIES		
e) Lecturing		
- Course 'Stofwisseling' at medical faculty, Radboud University, Nijmegen	2011	2.0
TOTAL		**33.3**