

UNDERSTANDING PAIN PROCESSING IN CHRONIC PAIN PATIENTS USING NEUROIMAGING TOOLS

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Abstract**USING NEUROIMAGING TOOLS TO UNDERSTAND
PAIN PROCESSING IN CHRONIC PAIN**

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The purpose of this thesis was to investigate whether chronic inflammatory pain changes the function and the structure of the central nervous system in rheumatoid arthritis (RA) patients. We wanted to determine what are the neurobehavioural correlates of improvement after treatment with tumor necrosis factor (TNF) inhibitors, and whether functional magnetic resonance imaging (fMRI) could be used as a marker of treatment efficacy. We recruited RA patients due to begin anti-TNF and age- and gender-matched controls. We demonstrated that despite being perceived as equally painful, pressure stimuli result in more extensive brain activation mainly in the regions involved in stimulus-oriented attention and self-referential processing. We also confirmed that there is a reduced brain response to experimental heat stimuli in RA in comparison to healthy controls. We were able to demonstrate, using fMRI, short-term effects of treatment. Patients, who were classified as responders, showed a greater decrease in activation mainly within limbic regions, as well as the ipsilateral insular cortex. These regions were more activated at baseline, offering a possible future marker of treatment efficacy. At the long-term visit, anti-TNF treatment resulted in a marked clinical improvement, as well as normalisation of the brain-activation in response to evoked pain. A decrease of activation in response to pressure was observed mainly in the limbic regions. We suggest that amygdala and hippocampus mediate the effect of TNF inhibition on pain behaviour and depression. The morphometric results show that there is an increase in grey matter concentration in the basal ganglia. We hypothesise that this effect is due either adaptation to pain processing or to altered movement control as movement is affected in RA. Moreover, brain volume was smaller in RA patients. It is not clear whether these changes represent accelerated atrophy, the effect of systemic inflammation, or rather intrinsic differences between RA patients and healthy controls. Future studies should focus on early RA and work to identify biomarkers that indicate likely treatment responders, as early successful interventions in treating RA are thought to be key to longer positive outcomes.

Acronyms and abbreviations

Anatomical abbreviations

- ACC – anterior cingulate cortex
- CNS – central nervous system
- DLPFC – dorsolateral prefrontal cortex
- IC – insular cortex
- M1 – primary motor cortex
- mPFC – medial prefrontal cortex
- PAG – periaqueductal grey
- PFC – prefrontal cortex
- PCC – posterior cingulate cortex
- RVM – rostral ventromedial medulla
- S1 – primary somatosensory cortex
- S2 – secondary somatosensory cortex
- SMA – supplementary motor area

Other acronyms and abbreviations

- ASF – Atlas Scaling Factor
- Anti-TNF – anti-tumour necrosis factor
- BET – Brain Extraction Tool
- BDI - Beck Depression Inventory
- BOLD – Blood Oxygenation Level Dependent
- CSF – cerebro-spinal fluid
- CON_{BL} – controls at the baseline visit
- CON_{ST} – controls at the short-term visit
- COPE – Contrast of Parameter Estimates
- CRP – C-reactive protein
- DAS28 – disease activity score in 28 joints
- DMARD – disease modifying antirheumatic drug

- DNIC – diffuse noxious inhibitory control
- EPI – Echo Planar Imaging
- ESR – erythrocyte sedimentation rate
- EULAR – the European League against Rheumatism
- FEAT – FMRI Expert Analysis Tool
- FID – free induction decay
- FILM – FMRIB’s Improved Linear Model
- FLAME – FMRIB’s Local Analysis of Mixed Effects
- FLIRT – FMRIB’s Linear Image Registration Tool
- FNIRT – FMRIB’s Non-linear Image Registration Tool
- fMRI – functional magnetic resonance imaging
- FSL – FMRIB Software Library
- FWHM – full width half maximum
- GLM – General Linear Model
- HPA – hypothalamic-pituitary-adrenal axis
- ICV – intracranial volume
- IQR – interquartile range
- IL - interleukin
- MCFLIRT – Motion Correction using FMRIB’s Linear Image Registration Tool
- MMSE – Mini Mental State Examination
- MNI – Montreal Neurological Institute
- MRI – Magnetic Resonance Imaging
- NRS – numerical rating scale
- NSAID – non-steroidal anti-inflammatory drug
- PGIC – Patient Global Impression of Change
- PCS - Pain Catastrophising Scale
- PET – Positron emission tomography
- PAT_{BL} – patients at the baseline visit
- PAT_{ST} – patients at the short-term visit
- PAT_{LT} – patients at the long-term visit

- PE – parameter estimate
- RA – rheumatoid arthritis
- rCBF – regional cerebral blood flow
- SD – standard deviation
- TE – time to echo
- TI – inversion time
- TNF – tumour necrosis factor
- TR – repetition time

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Chapter 2

METHODS

2.1 Methodological background

2.1.1 Introduction

Magnetic resonance imaging (MRI) is a multi-modal imaging technique that may be used to study brain structure as well as the dynamics of neurophysiology that accompany brain function. It is non-invasive and does not require exposure to ionising radiation or radioactive tracers; therefore, it can be used for repeated measurements in longitudinal studies.

2.1.2 Functional Magnetic Resonance Imaging

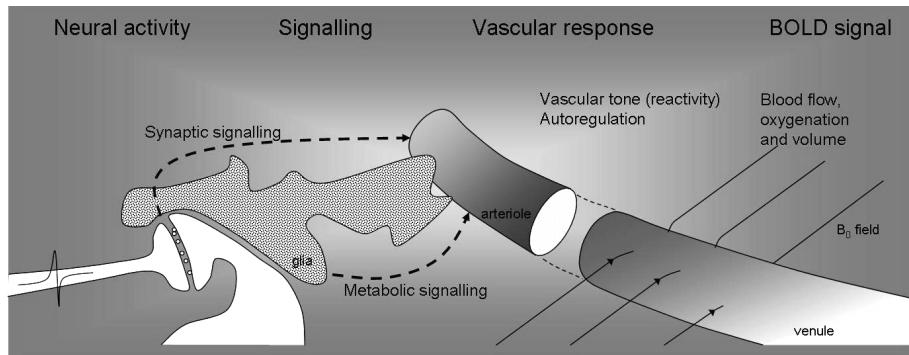
Functional magnetic resonance imaging is used to study neurophysiological correlates of behaviour by determining which brain regions become more active during stimulation. In this thesis, a blood oxygenation dependent contrast (BOLD) functional magnetic resonance technique was used and it will be subsequently referred to as functional magnetic resonance imaging (fMRI).

2.1.2.1 Physiological correlates of brain electrical activity

Neuronal activation is associated with an increased consumption of oxygen and glucose. An increased metabolism is accompanied by an increase in the regional cerebral blood flow (rCBF) and regional cerebral blood volume (rCBV), that deliver glucose and oxygen and remove carbon dioxide and heat from the tissue. There is an oversupply in cerebral blood relative to an increased demand for oxygen as during the brain activation the cerebral metabolic rate of oxygen increases less (5-25%) than the rCBF (20-70%) and rCBV (5-30%) (Buxton, 2002).

At rest, only about 40% of the delivered oxygen leaves the capillaries and is used for metabolism. This ratio is called the oxygen extraction fraction. During neuronal activity, the velocity of the rCBF increases resulting in a shorter blood transit time, and a smaller relative amount of oxygen available for tissues (approximately 30%) (Buxton et al., 2004; Buxton, 2002).

Fig. 2.1: Neuro-vascular coupling



Interactions between the neural activity, synaptic and metabolic signalling, the vascular response, and the BOLD signal (from (Wise and Tracey, 2006)).

2.1.2.2 Regulation of cerebral blood flow

There is a very high correlation between the rCBF change and neuronal activity both in terms of the amount of change and the spatial location. The increase of the rCBF and

rCBV during brain activation is caused by dilation of arterioles, which leads to an increase in blood flow velocity without changes in blood pressure (Buxton, 2002). The mechanisms controlling the rCBF are not fully understood, and the rCBF is not directly regulated by use of energy, oxygen or glucose (Mintun et al., 2001) nor products of the metabolism (Pinard et al., 1984). It has been suggested that the rCBF may be controlled by the neurotransmitters or other signalling molecules such as calcium ions or adenosine. The rCBF may also be controlled by the nerve fibres innervating cerebral vessels (Buxton, 2002; Attwell and Iadecola, 2002) (Figure 2.1).

2.1.2.3 Blood Oxygenation Level Dependent contrast

Oxyhaemoglobin is diamagnetic and has a similar magnetic susceptibility as the surrounding tissue. Deoxyhaemoglobin is paramagnetic and creates a magnetic gradient inside and around the erythrocytes. This gradient causes local susceptibility changes, increases dephasing, and shortens both T2 and T2* times (Thulborn et al., 1982). Therefore, haemoglobin may be used as an endogenous contrast agent (Ogawa et al., 1990; Kwong et al., 1992; Ogawa et al., 1992).

During brain activation, one would expect the level of deoxyhaemoglobin in the blood to increase as a result of the increase in brain metabolism. However, there is actually a drop in deoxyhaemoglobin concentration because during the neural activity, the rCBF and rCBV increases more than cerebral metabolic rate of oxygen (Buxton, 2002). Subsequently, relatively less oxygen is removed from the blood as the cerebral blood flow increases, delivering more oxygenated haemoglobin and reducing the concentration of deoxyhaemoglobin. This results in an increased ratio of diamagnetic oxyhaemoglobin to paramagnetic deoxyhaemoglobin on the venous side of the local vascular bed compared to when the brain was at rest (Buxton, 2002). This results in less field-altering effect from deoxyhaemoglobin, reduced dephasing of the MR signal and a higher intensity on the T2*-weighted image. This is the phenomenon that the BOLD contrast is based on.

The image intensity depends on the changes in the rCBF, cerebral metabolic rate of oxygen, and the rCBV (Buxton et al., 2004; Jezzard and Buxton, 2006), as well as the rest-

ing cerebral blood volume and the regional micro-vascular anatomy (Boxerman et al., 1995; Bandettini et al., 1997). Therefore, BOLD-fMRI is not suitable for quantitative measurements of brain activation.

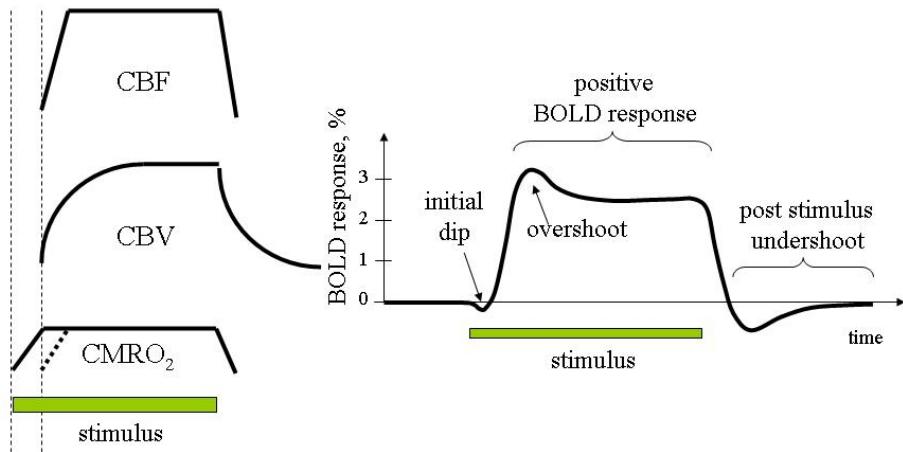
2.1.2.4 Haemodynamic response

fMRI measures neural activity indirectly, using the haemodynamic response as a surrogate. The haemodynamic response (occurring over seconds) is much slower and smoother than the neuronal response (occurring over tens to hundreds of milliseconds). There is also a delay of between 4–6 seconds between the onset of the stimulus and the peak of the haemodynamic response due to the mechanical properties of the vessels (Mandeville et al., 1999). After the onset of activation there is an initial “overshoot” of 2–3 seconds as the metabolism increases, producing more deoxygenated haemoglobin, but the rCBV has not yet reached the steady-state (Figure 2.2). This is followed by changes in the rCBF until a steady-state is reached resulting in a plateau in response. After the end of the stimulus the rCBF returns to a baseline faster than the rCBV, leading to a post-stimulus undershoot (Mandeville et al., 1999; Buxton, 2002). There are two alternative hypotheses explaining the undershoot: (1) the cerebral metabolic rate of oxygen returns to baseline slower than the rCBF (Frahm et al., 1996); (2) the rCBF falls below baseline at the end of stimulation due to inhibition and a decrease in neuronal activity (Logothetis, 2003).

2.1.2.5 Neuronal activity and BOLD signal

The interpretation of BOLD signal is not straightforward, as it is an indirect measure of neuronal activity, and does not represent a single neurophysiological phenomenon. BOLD signal is sensitive to large populations of neurons (Logothetis et al., 2001), and the signal changes are most pronounced in the regions of the cerebral cortex with higher synaptic density (Buxton, 2002). The signal intensity change mainly reflects the excitatory input to neurons (Ogawa et al., 1993), and the synaptic processing rather than the neuronal output (Logothetis et al., 2001). From studies in primates it is known that most

Fig. 2.2: BOLD response



Changes in the regional cerebral blood flow (rCBF), regional cerebral blood volume (rCBV), and cerebral metabolic rate for oxygen (CMRO_2) contributing to BOLD response.

of the energy is used by postsynaptic processes (74% of the total energy), whereas action potentials use approximately 10% of the energy, and neuronal resting potential uses 2% (Attwell and Laughlin, 2001).

BOLD changes do not allow us to distinguish between activation of excitatory and inhibitory neurons. However, it is assumed that an increase in the signal is a result of excitation rather than inhibition, as inhibitory neurons contribute to the BOLD signal to a lesser degree. These neurons are less numerous, with only 15-30% of neurons being inhibitory (Waldvogel et al., 2000), and are metabolically less demanding because they have fewer synapses and less steep action potentials (Nudo and Masterton, 1986). On the other hand, a decrease of BOLD signal may reflect both reduction in neuronal activity and haemodynamic changes independent of changes in neuronal activity (Shmuel et al., 2002). Moreover, the negative BOLD response, i.e., “deactivation”, has been associated with inhibitory processes (Seitz and Roland, 1992).

2.1.2.6 Spatial and temporal resolution of fMRI

In fMRI, spatial resolution depends on the spatial extent of the haemodynamic response (Moonen and Bandettini, 2000), the sensitivity of an experiment as well as the magnetic field strength and the coil configuration (Norris, 2006). The typical extent of activation for human brain imaging studies is about 3 mm (Norris, 2006; Jezzard et al., 2001). Temporal resolution of fMRI is about 500 ms, although theoretically it can be 50 ms. The main limiting factor is the haemodynamic response to neuronal activity which usually takes 4-8 s to rise to full amplitude. Other factors include T1-recovery time of magnetisation for EPI which is usually 1-1.5 s, speed of image acquisition, and also the variability in the response time between subjects, tasks, and brain regions (Moonen and Bandettini, 2000).

2.1.2.7 Design of an fMRI experiment

In functional imaging experiments, percentage BOLD signal changes are less than 10% (Buxton, 2002). Therefore, in order to improve the signal to noise ratio the stimulus has to be repeated, and the responses are averaged.

In the block design, relatively long periods of stimulation are alternated with periods of rest (Figure 2.3). This paradigm is robust and statistically efficient when detecting the BOLD response (Liu et al., 2001), therefore, it was used in this study for the control task.

In the event-related design, the stimuli are short and the duration of rest periods (called inter-stimulus intervals, ISIs) can vary (Figure 2.4). The advantages of the event-related design are that it minimises the physiological noise, as the stimuli are delivered randomly over time, and are not synchronous with physiological cycles. Moreover, this design makes it possible to detect transient changes. As the duration of rest intervals is varied, the participants are not able to predict when the next stimulus is applied. The main disadvantage is that this model is statistically less efficient than a block design; therefore, it requires many repetitions of stimulation. This design was used during the noxious stimulation, as it reduced expectation, habituation as well as the risk of sensitisation to stimuli.

Fig. 2.3: Haemodynamic response and stimulation timing in a block design experiment

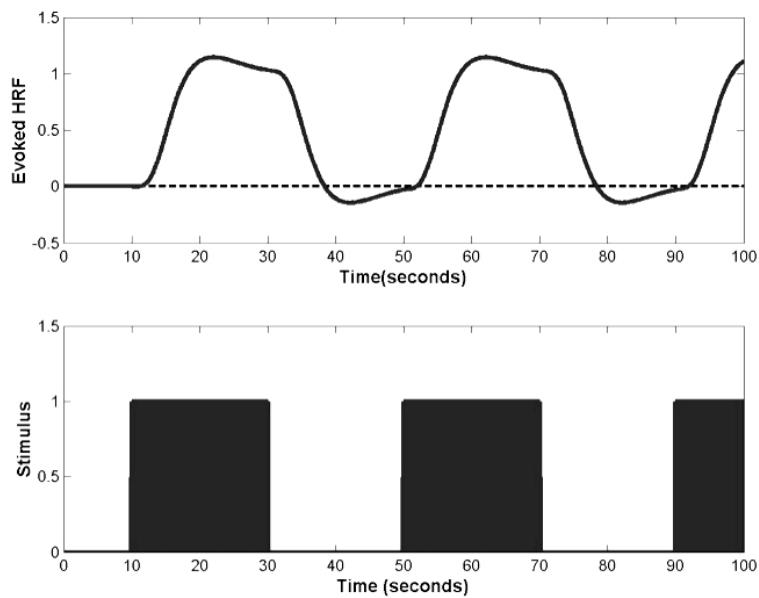
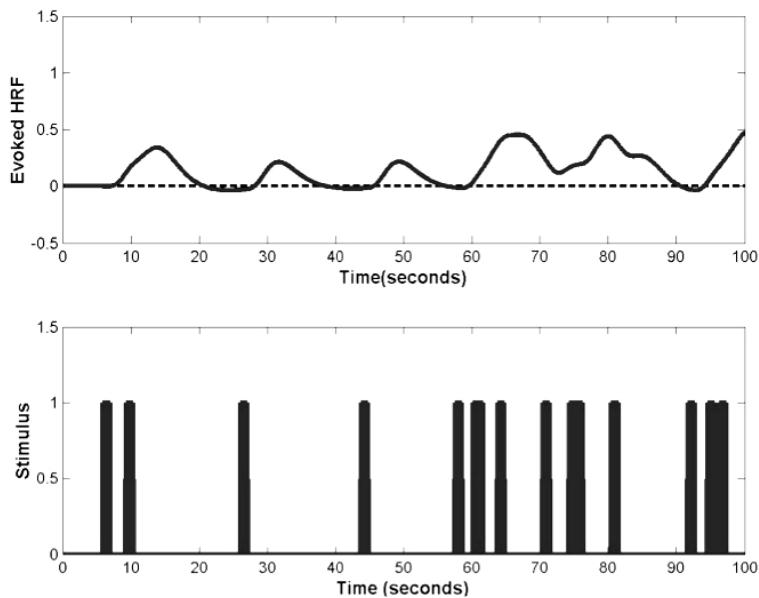


Fig. 2.4: Haemodynamic response and stimulation timing in an event-related design experiment



2.2 Study Protocol

This was a prospective, observational study in patients with active RA, who were due to begin the anti-TNF treatment.

Patients were scanned three times. The first visit, i.e., the baseline, took place before the start of the anti-TNF treatment (PAT_{BL}). The second visit was between two and four weeks after the first drug dose, in order to assess the short-term treatment effects (PAT_{ST}). The last visit was scheduled between six and ten months after the start of the therapy in order to study the long-term effects of the treatment (PAT_{LT}) (Figure 2.5). The time windows were chosen on the basis of the clinical studies which demonstrated that the improvement from baseline reaches its maximum within the first four weeks (Feldmann et al., 1996), and the treatment effects are stable after six months (Kievit et al., 2009).

Age- and gender-matched healthy volunteers were recruited as a control group. Controls were scanned at the baseline (CON_{BL}), and at the follow-up visit between six and ten months after the baseline (CON_{FU}). The control subjects were scanned twice in order to account for any learning, conditioning or expectation effects.

2.2.1 Participants

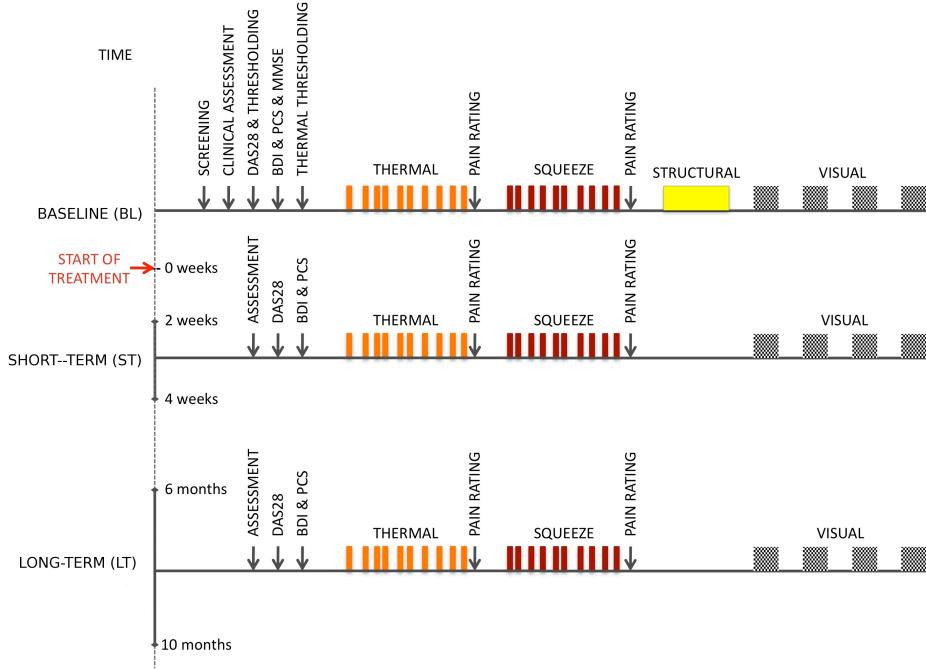
RA patients due to start the anti-TNF treatment were consecutively recruited from the Department of Rheumatology, Nuffield Orthopaedic Centre, Oxford.

Suitable patients were first approached by their treating consultant, either during a regular outpatient appointment or during patients' stay at the clinic. If patients expressed an interest in the study they were given the Patient Information Sheet and asked for their permission to have their contact details given to the researcher.

Healthy volunteers were recruited via poster advertisement and they contacted the researcher via phone or email.

The researcher contacted the potential participants by phone to check their suitability for the study. If a volunteer was willing to participate, an appointment was arranged.

Fig. 2.5: Study outline showing the experimental procedures performed at each of three visits in the patient group



Patients were asked not to take any painkillers 24 hours before the scanning session, but other medication was not altered.

All the scans were done using the 3T Siemens Tim Trio MR scanner located at the Oxford Centre for Functional Magnetic Resonance Imaging (OCMR) in the John Radcliffe Hospital, Oxford. The study was approved by the Oxfordshire Research Ethics Committee and conducted in accordance with the principle of the Declaration of Helsinki. A written informed consent was obtained from all the participants at the beginning of the first visit.

2.2.2 Inclusion and exclusion criteria

The following inclusion criteria were used for the patient group: active rheumatoid arthritis, age between 25 and 80 years. The exclusion criteria were: (I.) history of neurological or psychiatric disease other than depression, as depression and anxiety-related disorders show an overlap with chronic pain syndromes (Bair et al., 2003), (II.) any medical condition that could affect the results of the study, (III.) any medication acting on the central nervous system either as a treatment or for recreational use, (IV.) contraindications for MRI.

The inclusion criteria for healthy volunteers were an age between 25 and 80 years and overall good health. The exclusion criteria for the control group were: (I.) chronic or recurrent pain, especially one requiring medication, (II.) any medical condition that would affect the results of the study, (III.) medication acting on the central nervous system either as treatment or for recreational use, (IV.) contraindications for MRI.

2.2.3 Sample size

The sample size depends on the statistical power, i.e., the probability of rejecting the null hypothesis when it is not true. The sample size has to be large enough to detect when the null hypothesis should be rejected.

From the literature (Desmond and Glover, 2002) it is known that at least 12 subjects per group are required to achieve necessary power (80%) for the statistical analysis. However, their estimates were based on a block design task and may not be generalised to event-related designs. Murphy and Garavan (Murphy and Garavan, 2004) suggested that sample size typically used in fMRI studies, i.e., between 10 and 20 subjects is too small and the studies are usually underpowered. They demonstrated that at least 58 subject were required for sufficient power. However, Murphy and Garavan demonstrated that although the studies with 10–20 subjects were likely to have many false positives, they were not inaccurate and that most of activated areas were true positives.

More subjects lead to an increased sensitivity to an effect, and better generalisability of the results to the whole population. In patient studies, the sample size is usually small because of limited patient access (Mazziota et al., 1997).

In this study, we have recruited a sufficient number of patients so that there was at least 12 patients who continued the treatment for over six months, and attended all three visits.

2.2.4 Study medication

Currently, there are three TNF inhibitors registered in the UK for treatment of active RA: Etanercept (Enbrel[®], Wyeth), Infliximab (Remicade[®], Schering-Plough) and Adalimumab (Humira[®], Abbott). In the UK this medication is recommended for use in highly active RA in adults who failed to respond to at least two disease-modifying antirheumatic drugs, including Methotrexate, or who did not tolerate Methotrexate.

Patients who took part in this study were treated with all of these drugs. Patients were asked not to take their analgesic drugs 24 hours before the scan. As this was an observational study no medication, apart from NSAIDs, was altered by the researchers.

2.2.5 Baseline assessment

During the first visit, all participants underwent a medical and a MRI-safety screening, and psychological assessment. A thresholding was performed to determine the strength of painful stimulations used during imaging.

2.2.5.1 General screening

At the beginning of the first visit the researcher confirmed that the participants did not have any contraindications for an MRI scan, and that they fulfilled the inclusion and exclusion criteria. All subjects underwent a medical interview during which they were

asked about their health, especially chronic diseases requiring medication, chronic or recurrent pain conditions or any other condition that might affect the study.

2.2.5.2 Clinical assessment of the patient group

In the patient group the pre-scanning assessment was extended. Patients were asked about their medical history including disease duration, comorbidities including other pain conditions, depression and medication, including the type and number of DMARDs and analgesics. The daily pain intensity and disease activity were also assessed.

Pain assessment

In this study, the 11-point verbal Numerical Rating Scale (NRS) was used for self-reported assessment of pain. The anchors were: 0 = "no pain" and 10 = "the worst pain imaginable".

At the beginning of each visit patients were asked for an average daily pain intensity over the past four weeks or since the last visit if less than four weeks. This approach has been used previously in a study by Gracely and colleagues (Gracely et al., 2004).

The pain intensity is the most important pain dimension for patients and has been shown to be the main factor contributing to treatment outcome (Morley et al., 1999). In patients with chronic musculoskeletal pain, uni-dimensional pain intensity ratings reflects mainly the sensory aspect of pain, and the affective predictors do not contribute to NRS ratings (Huber et al., 2007). Uni-dimensional scales has been recommended for use in pain assessment (Cruccu et al., 2004). The NRS has been demonstrated to be clinically relevant in clinical trials (Salaffi et al., 2004), and more reliable than the Visual Analogue Scale (VAS) (Ferraz et al., 1990).

In our study, patients were also asked about the duration of stiffness of their joints on waking in the morning, as this symptom is associated with pain in RA (Fields and Martin, 2005).

Disease activity

Disease activity was assessed using the Disease Activity Score in 28 joints (DAS 28) (Prevoo et al., 1995). This is a combined index of overall disease activity. It includes four items: tender joint count (TJC), swollen joint count (SJC), laboratory markers of inflammation, i.e., the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), and the patient's rating of the subjective general health (GH) over the last seven days using the 100 mm Visual Analogue Scale. $DAS28 = 0.56\sqrt{TJC} + 0.28\sqrt{SJC} + 0.70\ln(ESR) + 0.014(GH)$. DAS28 is a continuous scale with a normal distribution, where the higher value indicates higher disease activity.

As a composite measure, the DAS28 is more clinically valid at assessing a disease activity than a single measurement alone, because it better reflects the complex nature of RA. It is also more sensitive to change because it is more precise as a composite measure and so has less variability than the individual measures it includes (Neogi and Felson, 2008; Fransen and van Riel, 2005). The DAS28 is suitable for quantitative analysis, and comparing the disease activity in the same patient at another time point or between patients (Smolen and Aletaha, 2008). DAS28 has been validated as an outcome measure (Prevoo et al., 1995) and has been demonstrated to differentiate between high and low disease activity (van Riel and van Gestel, 2000). The DAS28 is applicable in clinical trials and clinical practice. It can be used to assess disease activity state, as well as improvement of disease activity (Smolen and Aletaha, 2008).

Joint tenderness and swelling provide the most specific measures to assess inflammatory activity in RA, and are the most important measures of clinical status (Pincus et al., 2007). Swollen joint count is a clinical method of quantifying the amount of inflamed synovial tissue and effusion, whereas tender joint count is more closely associated with the intensity of pain (Naredo et al., 2005). The correlation between the tender and swollen joint count is weak (Scott et al., 2003).

Both inflammatory markers, ESR and CRP, are similar and their results are correlated. ESR is believed to be a better test to measure general severity of RA than CRP, because it is sensitive to immunoglobulins and rheumatoid factor, even though it is a poorer measure

of acute inflammation (Wolfe, 1997). ESR increases with age, independently of disease activity, but for the DAS28 higher than 3.2, the effect of age and gender is not significant (Radovits et al., 2007).

In this study, 28 joints were assessed first for swelling, then for tenderness. Subsequently a patient was asked for a rating of the general health. The blood samples for ESR and CRP were taken at the end of each visit to avoid the effect of a venepuncture pain on scanning session.

2.2.5.3 Psychological assessment

All participants were asked to complete the Beck Depression Inventory and the Pain Catastrophising Scale questionnaires to assess their depressive mood and catastrophising tendencies respectively, as both depression and catastrophising influence the pain experience (Giesecke et al., 2005; Gracely et al., 2004). Moreover, all patients were screened for cognitive impairment using the Mini Mental Status Exam (MMSE) (Folstein et al., 1975).

Beck Depression Inventory

The Beck Depression Inventory (BDI) (Beck et al., 1961) is a measure of the behavioural symptoms of depression and general emotional distress. It is a self-report questionnaire, measuring the severity of the symptoms during the last week. It consists of twenty one items, where each one corresponds to a specific category of depressive symptom. Each item is presented in multiple choice format with four statements rated on a scale from 0 to 3. The total score range is 0 to 63, with higher scores indicating higher levels of depression. The standard cut-offs for the BDI are: 0-9 "*no depression*", 10-18 "*mild*" to "*moderate depression*", 19- 29 "*moderate*" to "*severe depression*" and 30-63 "*severe depression*". The BDI demonstrates a high reliability and validity in psychiatric and non-psychiatric populations (Beck et al., 1961), including the chronic pain population (Morley et al., 2002). It is suitable for monitoring changes over time, and it is recommended for use in research as well as in clinical settings.

The BDI in the chronic pain population may be difficult to interpret as some of the items refer to physical complaints that in these patients may be caused by the chronic pain condition rather than a depressed mood. In chronic pain patients the total BDI score may be inflated by the items related to somatic complaints (Williams and Richardson, 1993; Campbell et al., 2003; Peck et al., 1989). Nevertheless, the BDI is valid to discriminate between chronic pain patients with and without major depression, and removing the somatic items does not improve this (Geisser et al., 1997).

Pain Catastrophising Scale

Catastrophising is recognised as a separate construct from depression (Geisser et al., 1994; Sullivan et al., 2001a). It affects response to pain and accounts for 7% to 31% of variance in pain ratings (Geisser et al., 1994).

The Pain Catastrophising Scale (PCS) is a tool to measure the tendency to focus on pain, exaggerate the threat value of pain and negatively evaluate one's ability to deal with pain (Hirsh et al., 2007). It is a self-administered tool,³ which consists of thirteen items rated on a scale from 0 to 4, with the total score range from 0 to 52, and higher scores reflecting a higher level of catastrophising. The PCS is usually treated as a continuous, normally distributed variable without a cut-off value (Sullivan et al., 1995, 2001b). It can be divided into three subscales: rumination about pain, magnification of pain-related symptoms and feeling of helplessness about pain-related outcomes (Sullivan et al., 1995). Helplessness is a particularly important factor in adjustment to pain, and disability in patients with arthritis (Keefe et al., 2002). The PCS also has a good internal consistency and test-retest reliability in pain patients (Osman et al., 2000).

Mini Mental Status Exam

The Mini Mental Status Exam (MMSE) (Folstein et al., 1975) is used to screen participants for cognitive impairment, as dementia may affect pain ratings and the patients' cooperation during the study. The maximum score is 30 and the cut-off value for dementia is

23/24 (Anthony et al., 1982). Mild cognitive impairment is a cognitive disturbance recognized with an objective memory deficit and the MMSE score below 24 and there is (Rivas-Vazquez et al., 2004).

2.2.6 Follow-up assessment

2.2.6.1 Patients

At the subsequent visits patients were asked about the effects of the anti-TNF treatment, including general health and pain. The disease activity was assessed using the DAS28, in the same way as at the baseline visit. Patients also completed the psychological questionnaires (BDI and PCS). The improvement was assessed using the Patient Global Impression of Change scale and the EULAR clinical criteria.

Patient Global Impression of Change

The Patient Global Impression of Change (PGIC) was used to assess the clinical importance of the subject's improvement or worsening compared to the baseline (Dworkin et al., 2005). Patients were asked to complete the sentence "*Since my last visit, my overall status has:*" and the possible answers corresponded to rating on a seven-point categorical scale from plus three, corresponding to "*Very much improved*", to minus three, "*Very much worse*". The concept of *much improved* is conceptually reasonable, and clinically relevant and it is believed to assess the patients overall status including the effect of treatment, side effects and expectations (Buchbinder et al., 1995).

Improvement and response

Improvement was defined as a change in the DAS28 score larger or equal to 1.2 (van Riel and van Gestel, 2000). A simplified criterion was used as it encompasses those who

achieved good and moderate EULAR response. This approach was used previously by Pocock and colleagues (Pocock et al., 2008).

The European League Against Rheumatism (EULAR) criteria were used to assess response to treatment. These criteria are based on the DAS28 and include both a change in disease activity and the current disease activity (van Gestel et al., 1999). To be classified as good responders patients needed to have a significant reduction of DAS28, as well as low current disease activity (van Riel and van Gestel, 2000). There are three categories: good, moderate, and non-responders.

Patients were also assessed by their consultant at 3 months, and classified as responders or non-responders (van Riel and van Gestel, 2000). Patients, who were classified by their consultants as responders, were refereed to in this study as "responders at three months", and only those patients were assessed at the long-term.

Remission

Remission is a goal of the treatment. It is defined as an absence or a very low level of disease (Makinen et al., 2005). In this study, the DAS28 score below 2.6 was a criterion for remission (van Riel and van Gestel, 2000; Fransen et al., 2004; Makinen et al., 2008; Sokka et al., 2008; Kristensen et al., 2008).

2.2.6.2 Controls

At the follow-up visit, control subjects underwent a short medical interview to confirm that there were no changes in their health status since the baseline visit. They were also asked to complete the psychological questionnaires.

2.2.7 Stimulation

There were two types of painful stimuli, pressure and heat, and in addition there was a visual stimulation.

2.2.7.1 Pressure stimulation

Mechanical pressure was chosen as stimulation because joint tenderness on pressure has been demonstrated to be one of the characteristics of RA. Moreover, deep pain evoked by pressure stimuli is highly associated with musculoskeletal pain (Geisser et al., 2007; Diatchenko et al., 2005; Lautenbacher et al., 1994). Although this pain is disease-related, it is not a clinical pain, as it is experimentally evoked. Deep pain has been used previously for quantifying analgesic drug effects (Enggaard et al., 2001; Fillingim et al., 2004; Loetsch and Angst, 2003).

During mechanical stimulation the most painful joint of a patient's right hand was pressed with a purpose-built, MRI-compatible pressure device (Figure 2.6). The device was semi-quantitative, and allowed for graded stimuli to evoke similar pain ratings in patients with different levels of joint tenderness. The pressure device consisted of a 1cm² rubber probe attached to a piston connected via a spring to a second piston with a scale from 1 to 6 inscribed on it. The most tender joint was chosen during the DAS28 assessment. The intensity was identified using the method of limits, i.e., the joint was pressed with increasing stimulus intensity until a patient reported strong pain (7–8 on the NRS) (Yarnitsky, 1997). The intensity of the stimulus was chosen to reliably evoke moderate pain, i.e., a pain rating of 5–6 on the 11-point NRS (Serlin et al., 1995). This stimulus intensity was used for the stimulation in the scanner for all visits, i.e., the intensity of stimulus was kept constant.

In the control group, the same pressure intensity was used as in the patient group. The controls received stimuli of the same intensity as patients of the same gender and similar age. Using moderately painful pressure in healthy people was not feasible in the fMRI experiment as the evoked pain did not attenuate quickly enough.

During the scanning session, the chosen joint was pressed with the same intensity ten times for 2 s. The duration of stimulus was chosen to produce reliable activation and to be adequate for reliable pain rating, but the pain diminished very quickly after the end of stimulation which is important in an event-related experiment. The interstimulus intervals were varied between 50 and 70 s to avoid expectation.

Fig. 2.6: The pressure-device used in this study



2.2.7.2 Heat stimulation

A painful heat stimulus was used as the experimental pain stimulus. Heat reliably activates brain areas associated with pain processing (Klein et al., 2005) and has been previously used in studies on analgesia (Fillingim et al., 2004; Luginbuhl et al., 2001).

A thermal stimulus is qualitatively different from a mechanical stimulus as it does not have the non-nociceptive, sensory component as the mechanical stimulus does. Moreover, as it is not related to the clinical pain in RA, it has a different context.

In this study, the thermal stimulation was delivered using an in-house built, MRI-compatible thermal resistor with a fast ramp time (from 30° to 60° Celsius in 0.8 s). The stimulation was triggered using an in-house built software, PainGain, that controlled the temperature, duration and timing of the stimuli. The software was driving the thermal resistor via a National Instruments PCMCIA-GPIB card (National Instruments, Austin, USA). The contact thermode area was 1.5 x 2 cm. The thermode was attached to the volar surface of a patient's right forearm, over the head of the brachio-radialis muscle to avoid veins and tendons. The stimulus was applied in a different place to the mechanical stimulus because patients could not tolerate the thermode attached over the inflamed joints.

The intensity of the stimuli was established outside the scanner using the following paradigm. The first stimulus was delivered at 48° Celsius, which was repeated to account

for habituation. The subsequent stimuli were applied approximately every minute, with temperature increasing by steps of 2° until a patient reported pain of 4 out of 10 on the NRS. Then the temperature was increased by 1° until a patient reported strong pain, 7-8 on the NRS. The maximum allowed temperature was 60° Celsius to avoid skin damage. The temperature resulting in a moderate pain, 5-6 on the NRS was repeated twice to confirm the ratings. The temperature was kept constant throughout the study.

In the control group, two intensities of heat were used: stimulation matched with the same temperature as in the patient group, and perception matched, i.e., evoking moderate pain in healthy controls. This approach has been used previously in other studies on chronic pain (Gracely et al., 2002; Giesecke et al., 2004).

During the scanning session the chosen stimulus was repeated 10 times. The stimulus duration was 2 s, the inter-stimulus interval was jittered between 50 and 70 s to allow effective sampling of the BOLD signal, and to avoid expectation. The intervals were long enough (over 50 s) to avoid sensitisation. The stimulation was appropriate to give reliable pain ratings and the pain diminished quickly after the stimulation ended.

2.2.7.3 Visual stimulation

The visual stimulus was used as a simple sensory paradigm to assess global, non-specific effects of medication on brain activation. There were 10 blocks of stimulation, i.e., black and white squared chequerboards flickering at a frequency of 8 Hz with a central fixation point, alternated with blocks of rest, i.e., a black screen with a fixation cross. The frequency of 8 Hz gives maximal physiological response (Kwong et al., 1992; Fox and Raichle, 1985). The visual stimulus was generated by the Presentation software version 11.0.

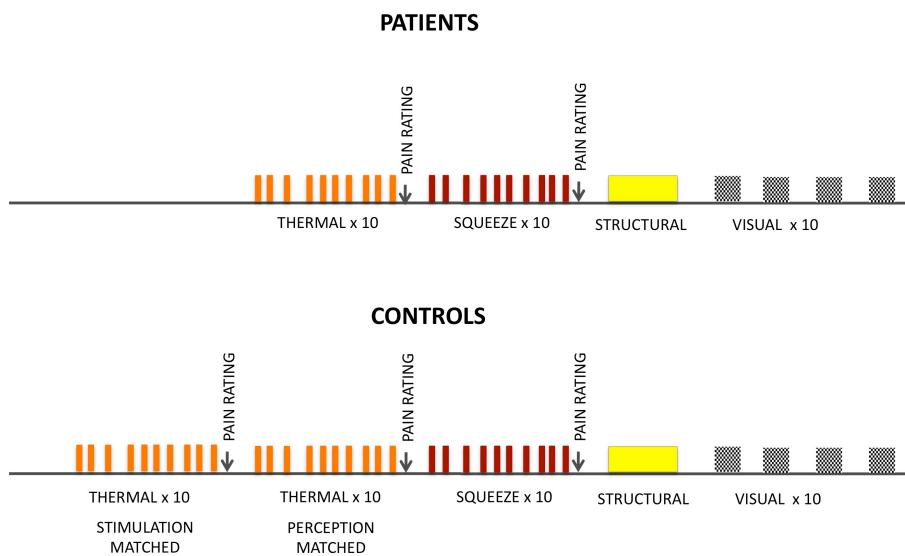
2.2.8 Scanning paradigm

Patients received two types of painful stimulation (Figure 2.7), pressure and heat, of the intensity chosen during the pre-scanning assessment. The order of the heat and pressure

stimulation was randomized and balanced across the patients. Controls received pressure stimuli and heat stimuli of the same strength as patients, i.e., stimulus matched as well as heat stimuli of the same perceived pain intensity as patients, i.e., perception matched.

Immediately after each scan subjects were asked to verbally rate the average pain intensity on the 11-point NRS. An average pain rating was used as the brain activation in response to all ten stimuli was averaged during the analysis, and also because we were not interested in analysing pain evoked by each individual stimulus. These average ratings were used for the subsequent statistical analysis. After the functional scans, the structural scan was acquired (during the baseline session only) for anatomical reference and morphometric analysis. The imaging session ended with a visual stimulation used as a control task to control for unspecific effects of treatment on the BOLD signal.

Fig. 2.7: Stimulation paradigm in the patient and control group at baseline



2.2.9 MRI data acquisition

MRI data were acquired on a 3T Tim Trio Siemens MRI scanner (Erlangen, Germany) using a single channel transmit-receive head coil.

A high resolution T1-weighted structural scan was acquired using an inversion recovery MP-RAGE sequence with the following parameters: TR = 204 ms, TE = 5.56 ms, inversion time TI = 1100 ms, flip angle 8°, rectangular field of view (FOV) 192x192mm, voxel size 1x1x1 mm. This image was used for subsequent registration of the functional data and as a reference for localisation of activation. This structural image was used for the morphometric analysis as it has a high spatial resolution and a good contrast between white and grey matter (Buxton, 2002).

fMRI data were acquired using a standard whole-brain gradient echo EPI sequence with the following parameters: TR = 3 s, TE = 30 ms, flip angle 90°, 36 axial slices covering the whole brain; field of view (FOV) = 192x256 mm, matrix size 64x64, voxel size 3x3mm in plane and 3.3 mm slice thickness. 195 volumes were acquired during the pain conditions and 102 volumes during the visual stimulation. The first two volumes, during which the steady state magnetisation has not been reached, were discarded leaving respectively: 193 and 100 volumes for analysis.

2.3 Data analysis

2.3.1 Analysis of fMRI Data

The fMRI data was analysed using FEAT (FMRI Expert Analysis Tool) version 5.98, a software tool for model-based fMRI data analysis. FEAT is part of the image analysis package FSL (FMRIB Software Library, www.fmrib.ox.ac.uk/fsl) version 4.1.4 (Smith et al., 2004).

2.3.1.1 Preprocessing

Before statistical analysis, the functional imaging data were preprocessed in order to remove artefacts and to prepare the imaging data so that the analysis was sensitive and statistically valid.

Brain extraction

Non-brain structures were removed from an image using BET (Brain Extraction Tool) (Smith, 2002), which is a part of the FSL package. BET uses the image intensity differences between the brain and surrounding tissues such as the meninges or skull. In this study the fractional intensity threshold (f) was set to 0.3 in order to increase the estimated brain outline and the vertical gradient in fractional intensity threshold (g) was set to -0.2 to decrease the outline at the bottom of the brain and give a larger outline at the top.

Spatial smoothing

Spatial smoothing was used to increase the signal-to-noise ratio without losing too much of the valid signal. It also improved the validity of parametric statistical tests, as the Gaussian Random Field theory used during the higher-level analysis is based on the assumption that the data are spatially smooth. Smoothing was done on each volume of the fMRI data by convolving the data with a Gaussian kernel of a full width at half maximum (FWHM) of 5 mm. Larger kernel sizes are recommended by some researchers for patient studies because of a bigger spread in the location of the activation (Price et al., 2006). However, as the kernel size should not exceed the expected activation area, e.g., the thalamic or brainstem nuclei, the kernel size was not increased in this study.

Intensity normalisation

In order to make the data comparable between subjects and sessions, the data were normalised to the same mean intensity by a single scaling factor resulting in a consistent mean between subjects. This is important for between-subjects comparisons, as otherwise the random effect analysis might misinterpret a greater mean as a greater activation.

Temporal filtering

Temporal filtering was used to remove the frequencies that did not contain any signal of interest, such as hardware-related drifts or physiological noise. The same filtering was applied to the model and to the data in order to maintain a match between them.

In this study, a high-pass filter cut-off of 100 s was used in order to remove low frequency artefacts, such as scanner-related drifts.

A low-pass filter was not used in this study. Although it increases the temporal smoothness of the data, it might potentially remove signal of interest, particularly in event-related experiments. Instead of a low pass filter, the temporal autocorrelation was removed using FILM (FMRIB's Improved Linear Model) (Woolrich et al., 2001), which is a part of the FSL package. This involved fitting the model, estimating the autocorrelation of the residuals, smoothing the autocorrelation estimates and constructing a "prewhitening" filter to "undo" the autocorrelation.

Motion correction

Motion is a serious problem in fMRI studies, especially in patient studies, as patients tend to be more restless than healthy subjects (Friston et al., 1996a). Moreover, motion tends to be more correlated with the task in patients than in healthy people (Bullmore et al., 1999). In a study by Seto and colleagues (Seto et al., 2001) there was twice as much head motion in patients as in age-matched controls and the older healthy controls moved twice as much as young adults.

Motion may be caused by head movements, swallowing, and physiological motion such as breathing, blood flow or cerebro-spinal fluid flow. Motion during image acquisition introduces artefacts as it causes mis-registration of image voxel locations within the brain structures. In functional imaging, blurring of an image is not a problem because the image acquisition is fast (30-50 ms). However, as the EPI sequence consists of a series of images, movement introduces changes in the local signal in the EPI time-series. When a subject moves, a signal from an individual voxel it does not correspond to the same point in space throughout the fMRI run (Buxton, 2002). This results in a local signal change

that leads to a false positive activation when the motion is correlated with the stimulus (Hajnal et al., 1994). Random motion may lead to false negative results by increasing the variance in the fMRI signal (Seto et al., 2001).

Motion in fMRI is a serious problem because typical signal changes associated with activation are only a few percent. Motion artefacts are one of the most important contributors to an fMRI signal unrelated to neural activity (Hajnal et al., 1995). These artefacts have to be corrected otherwise the variance due to motion will be attributed to activation or noise.

The best approach to reduce motion is to prevent it by stabilising the subject's head. After the data has been acquired, motion correction algorithms can be applied. For the analysis in this study, realignment was performed using MCFLIRT (Motion Correction using FMRIB's Linear Image Registration Tool) (Woolrich et al., 2001). This technique corrects for head motion by aligning all the EPI volumes with respect to each other using the rigid body transformation with 7 degrees of freedom, assuming that the head may change its position and size but not its shape (Jenkinson and Smith, 2001). In addition to the realignment, the motion correction parameters estimated by MCFLIRT (Jenkinson et al., 2002; Jenkinson and Smith, 2001) can be used as regressors of no interest in the subsequent data analysis (Friston et al., 1996a; Grootoorn et al., 2000). This approach has been shown to improve the statistics (Norris, 2006), although if many motion artefacts are highly correlated with the task, the regression of motion parameters may reduce the detected activation. However, without the correction there may be false positive activation (Friston et al., 1996a; Grootoorn et al., 2000).

In this study, motion parameters were used as a regressor in the model. Moreover, the volumes which were outliers with respect to motion were identified and removed by entering the additional regressor with 0 corresponding to the excluded volumes. This approach is based on the fact that in an event-related design the signal variation due to motion occurs earlier than the signal variation due to the real BOLD response. Therefore, it is possible to distinguish motion-induced signal change from the true activation (Birn et al., 1999).

2.3.1.2 First-level statistical analysis

The General Linear Modelling (GLM) was used to assess in which voxels the observed signal difference between the task and the baseline was really associated with the stimulation. The GLM is a regression model that estimates which combination of regressors related to the expected neural responses will result in the best fit between the model and the data at each voxel (Worsley and Friston, 1995). In the GLM, the time series in each voxel are modelled separately. The model can be represented as:

$$Y = \beta X + e \quad (2.1)$$

- where Y is the data, i.e., intensity values within a single voxel, β is a parameter estimate (PE), X is the model, and e is an error in the model fitting. A good fit between the activation and the model implies that the activation is indeed a result of the stimulation.

The first-level analysis is the analysis of time-series of the raw four dimensional fMRI data. The pre-processed fMRI data acquired during the pressure, heat or visual stimulation were entered into the model as the dependent variable (Friston et al., 1995). The model was generated from the timings of the stimulation used during the scanning session. As the BOLD signal is delayed in time with respect to the stimulation, the stimulus input function was convolved with a haemodynamic response function. This results in a slightly better fit for the whole model, reducing unexplained noise and increasing the statistical significance.

2.3.1.3 Higher-level statistical analysis

Registration

The higher-level analysis was used to test for differences between sessions or subjects. In order to combine data from several subjects or sessions the data were transformed into a standard anatomical structural space. The registration was performed using FLIRT

(FMRIB's Linear Image Registration Tool) (Jenkinson and Smith, 2001; Jenkinson et al., 2002) and FNIRT (FMRIB's Non-linear Image Registration Tool) (Andersson et al., 2008).

This was done in two steps. First, an example fMRI image was linearly registered to the brain-extracted structural image using a registration with seven degrees of freedom (rigid body transformation and global rescaling with single parameter). Then the structural image was registered to a standard image, a T1-weighted MNI 152 (Montreal Neurological Institute average of 152 brains) average image in standard space using twelve degrees of freedom (affine transformation that allows for scaling and skewing). Finally, for each subject, the two transforms were combined into a single transform that converted the low resolution EPI into the standard space. This transform was also applied to the first level statistical maps (activation parameters estimates and variance estimates) to transform them into the standard space so that all subjects' statistical data were in the alignment.

FNIRT was used after the FLIRT to non-linearly register subject's structural image to the standard space. FNIRT uses the original, non-BETed structural image as it requires skull as a reference. The warp resolution, i.e., the spacing between the warp field control points used in this study was 10 mm.

The non-linear registration is particularly important in the case of elderly patients with age-related brain atrophy and enlarged ventricles, as detecting average activation across subjects depends on good spatial registration of corresponding brain regions (Price et al., 2006).

Re-registration between visits

In our study patients were scanned at three separate occasions; therefore for each session the head position in the scanner was slightly different and the distortions in the EPIS slightly different for each session as the distortions depend on the exact position of a subject within the field.

Due to the local nature of the EPI distortions the rigid-body transform is not sufficient to adequately correct for these local distortions and to register an EPI image from the subsequent sessions. The best approach is to non-linearly unwarped each session using the

fieldmaps acquired at each session (with the same position as for the EPI). However, we did not acquire field-maps in this study. Instead we performed a non-linear registration of the EPIS from the follow-up sessions to the first session. Although, this did not remove the distortions caused by the subject's position in the brain, it resulted in all the sessions being in the same distorted space. This improved the alignment of anatomical structures between the sessions.

Typically, each functional image would be registered into the standard space separately so that the transform would be slightly different for each visit. In this study, the functional images from the follow-up sessions were registered to the functional images from the first session using firstly affine (FLIRT), and then non-linear (FNIRT) registration. Then this transform was combined with the transform mapping the functional images from the first session into the standard space, resulting in a single transform that mapped the functional images from the follow-up session to standard space. As a result of that the functional images from all three visits were registered together and only one transform was used to transform the functional images into the standard space. This step was performed on all first-level analyses before the higher-level analyses were done.

The analyses using the re-registered images resulted in slightly more extensive clusters in anatomically significant areas, but the activation pattern did not differ from the analysis using the standard analysis (Figure 2.8).

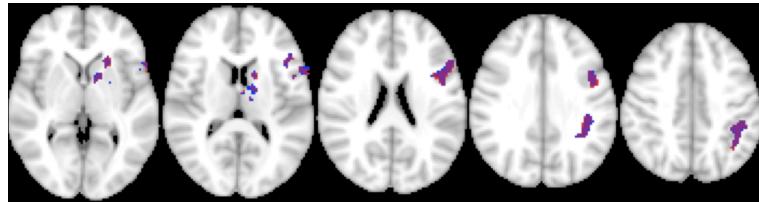
The results of re-registration were validated by visually inspecting the realignment of example functional images from the subsequent sessions.

It is not a standard approach to use a non-linear registration on the functional data. The linear registration models the overall differences in position and size between different brains but cannot account for local differences. The distortions in our data were mostly local and were located mainly in the frontal and parietal regions. Unlike the linear registration the non-linear registration allows local deformations as it uses the warp fields, i.e., fields of displacement.

The non-linear registration can significantly distort the original image. In order to keep the registration reasonable the gross structures of the image are registered first by registering a sub-sampled image. Then the warps fields are used as a start point for subsequent

registrations with a less sub-sampled. The regularisation is used to ensure that the warps are sensible as smoother warps are more likely to be appropriate and each point in the original space is expected to map only on one point in the transformed space.

Fig. 2.8: Higher level analysis results using standard and re-registered data



Higher level analysis. Difference in brain activation in response to heat-evoked pain in patients at the baseline and at the long-term visit. Mixed-effects analysis. $Z > 2.3, p < 0.05$. A standard analysis in red. An analysis using reregistered data in blue. Overlap in purple. Z range from 2.3 to 3.9 for both analyses.

Statistical analysis of the multi-subject and multi-session data

A fixed-effects analysis assumes that all subjects activate equally and it estimates within-session errors, ignoring cross-session or cross-subject variance. This analysis is more sensitive to activation than the mixed-effects analysis but allows for inferring only about the studied group.

A fixed-effects analysis was used to calculate the "difference COPEs" between visits, for each subject. The first-level results from the follow-up visits, e.g., the short-term visit (ST), were subtracted from the first-level results from the baseline visit (BL) resulting in a difference statistical map PAT_{BL-ST} (Figure 2.9). This analysis was performed for each subject, for each type of stimulation, for contrast baseline versus short-term visit and baseline versus long-term visit, separately. The resulting "difference COPEs" were used for subsequent analyses.

For comparison between the patient and control group or between visits within the same group of subjects a mixed-effects analysis was performed. This analysis uses the fixed-effects variances (i.e., the within-session across-time variance) and the random-effects variance (i.e., the across-session variance of first-level parameter estimates), there-

Fig. 2.9: Fixed-effects analysis model used to calculate the "difference COPEs"



fore it makes fewer assumptions about the data. In this study, both stages of the higher-level estimation method FLAME (FMRIB's Local Analysis of Mixed Effects) (Woolrich et al., 2004) were used for the higher-level analyses, i.e., the fast approximation was followed by more complex estimation processing of all voxels which where close to threshold. FLAME's results are considered valid for the population from which the subjects were drawn if the group size is larger than six subjects.

To test for a statistically significant difference between the patient and control group, an unpaired analysis, i.e., two-sample unpaired t-test, was performed (Figure 2.10). The results from the first-level analyses were entered into the model with patients and controls specified as separate groups to control for the difference in the cross-subject variance. A contrast for mean group difference was set in both directions, patients versus controls and controls versus patients.

To test for a statistically significant difference between visits, a two-sample paired t-test was used (Figure 2.11). The first-level results from the baseline and one of the subsequent visits were entered into the GLM. The first regressor modelled the visit, and the remaining regressors represented each subject.

In order to assess the mean effect of activation within a group, i.e., how group activates on average a one-sample t-test was used. To correlate the changes in the measured clinical or psychological variables with changes in pain-evoked brain activation, a higher-level analysis was used, in which the "difference COPEs" for each patients were entered into the GLM and the demeaned difference values for the measured variables were entered as additional regressors (Figure 2.12)

Fig. 2.10: A two-sample unpaired t-test

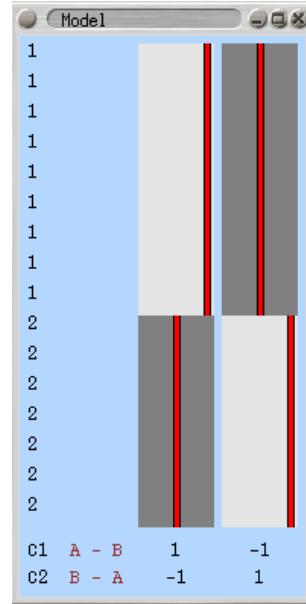


Fig. 2.11: A two-sample paired t-test

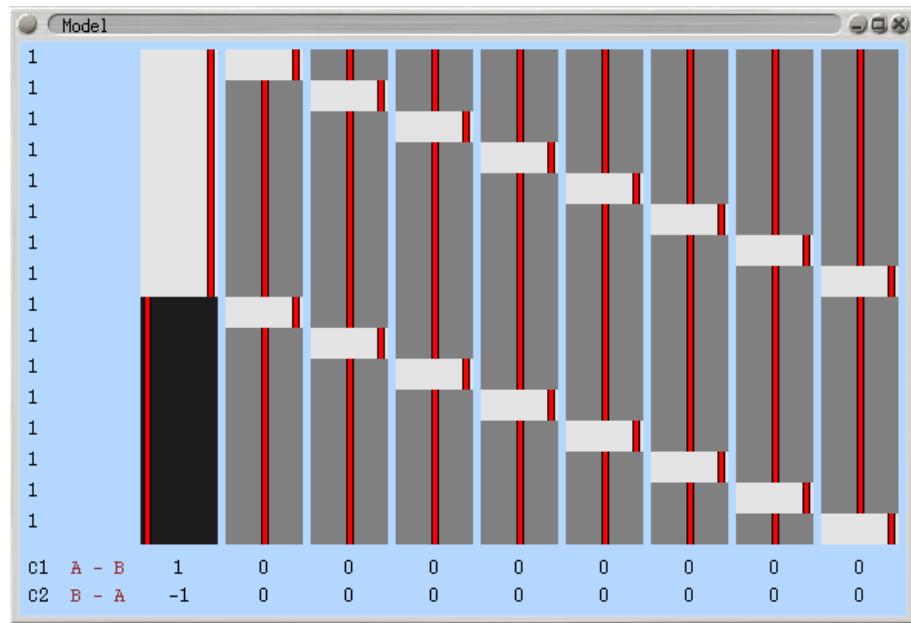
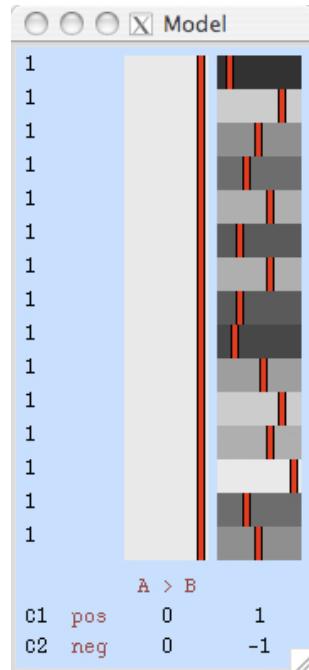


Fig. 2.12: Correlation analysis



2.3.2 Inference

The null hypothesis was that there was no difference between the stimulation condition and the rest condition, i.e., $\beta=0$ everywhere in the brain. Under the null hypothesis β is normally distributed. In order to convert PEs into a t-statistic image, the PE was divided by its standard error, which was derived from the residual noise after the complete model had been fitted. The t-image was then transformed into a Z statistic. Both t and Z statistics reflected how significantly the data was related to a particular regressor and were associated with a probability p . If the p -value was smaller than the p -threshold the voxel was assumed to be active as the null hypothesis was unlikely.

Statistical thresholding was used to find voxels active at a given level of significance. As there are tens of thousands of voxels in the image, sample thresholding at $p < 0.05$ would result in thousands of false positives. Therefore, the results were corrected for multiple comparisons. The Bonferroni correction is too conservative as the voxels are not

really independent from each other as the data are spatially smoothed at the earlier stage of the analysis or because the voxels may be located within the same neuroanatomical structure, therefore, they activate together. To reduce the number of false positives, the Gaussian Random Field Theory (GRF-theory) is used. The GRF theory assumes that the data is spatially smooth, therefore the number of independent measurements, so called RESELs (REsolution ELelements), is smaller than the number of data points in the original data.

In the cluster correction method, which was used in this study, a Z statistic map is thresholded at an arbitrary, set value of Z. The voxels which has passed the threshold are combined into contiguous clusters and the number of voxels in each cluster (spatial extent) was calculated. The GRF theory is used to estimate the probability of getting a cluster of a particular extent, given the spatial smoothness of the data and the Z threshold used, under the null hypothesis. Then each cluster's estimated significance level is compared with the specified cluster probability threshold to obtain significant clusters (Smith, 2004). Low Z threshold can violate GRF theory assumptions, but can detect clusters with a large spatial extent and a low Z. A high Z threshold gives more power to clusters with a small spatial extent and a high Z.

The advantage of the cluster-based method of correction is its sensitivity to activation, and the fact that it is more neurobiologically meaningful, as activation is expected to extend over several continuous voxels (Friston et al., 1996b). The disadvantage is that the Z threshold is arbitrary. This approach is not very good for localising small activation, as it is more powerful for activated regions that are large.

2.3.3 Analysis of the structural MRI

The structural data were analysed using FSL-VBM, a voxel-based morphometry style analysis (Ashburner and Friston, 2000) and FreeSurfer, a surface-based morphometry (Fischl and Dale, 2000).

2.3.3.1 FreeSurfer

FreeSurfer is a surface-based morphometric analysis technique (Dale et al., 1999; Fischl et al., 1999a,b), which is biologically meaningful, as it allows us to quantify changes with the respect to the anatomy of the folded cortical surface (Bernhardt et al., 2008).

Individual subjects' structural scans were linearly registered to the MNI 305 structural template using FLIRT, bias corrected, skull stripped using BET, and segmented into white matter, grey matter, and cerebro-spinal fluid (CSF). The segmented white matter was used to create a tessellated surface representing the grey-white matter boundary. The surface was then automatically corrected for topological defects and expanded to model the pial-grey matter boundary. The distance between the grey-white matter boundary and the pial-grey matter boundary was calculated at each point and used to estimate the cortical thickness. The grey-white surface mesh was inflated to minimise the distortions, and warped to match curvature features across subjects (Dale et al., 1999; Fischl et al., 1999a,b).

A study-specific template was generated from the curvature-based registration of all the subjects. Each subject's grey-white surface was inflated (Dale et al., 1999) and non-linearly registered to a study-specific surface template to match the sulci and gyri (Fischl et al., 1999b). After the registration, subject-specific cortical parcellations were created (Desikan et al., 2006). Subsequently, the thickness, volume, and area were calculated for each labelled region optimised for each subjects' specific curvature (Fischl et al., 2004). Each processing step was visually examined and verified.

A cross-subject GLM was fitted at each vertex to test group-wise differences in cortical thickness between patients and healthy volunteers. In order to control for age and gender effects, the participants were classified into four groups: male patients, female patients, male controls, and female controls, and the age was used as an additional continuous variable. Age and gender were controlled for as it has been demonstrated that both affect brain morphometry (Gur et al., 1999; Greenberg et al., 2008; Good et al., 2001).

The input for each group was separately modelled as a line with its own intercept and slope. This model implies that patients and controls could start at different cortical thick-

ness and the thickness could change at different rates. Two contrasts were investigated: firstly, between-group differences in cortical thickness (in millimetres) when controlling for age and gender, secondly between-group differences in age-related changes in cortical thickness (in millimetres per year). A t-test was used to test for differences between patients and controls.

Individual subjects' thickness measurements were smoothed using a full width half maximum (FWHM) kernel of 15 mm. The group difference t-stat maps were corrected for multiple comparisons across vertices using statistical procedures controlling for the false discovery rate at $p = 0.05$ (Genovese et al., 2002). A cluster-based thresholding method was also used to generate statistically significant differences. The Z-maps were thresholded at a vertex-wise threshold of $Z = 2$.

Global brain measures

Global brain measures were calculated for each subject in order to control the volume and thickness estimations for differences in brain size.

The Intracranial Volume (ICV) generated by the FreeSurfer was used to correct for differences in head size (Buckner et al., 2004). The total volume of segmented white and grey matter were also computed from the segmentation files. The total CSF volume was calculated as a sum of volumes of lateral ventricles, inferior lateral ventricles, third ventricle, fourth ventricle, fifth ventricle and the extra-ventricular CSF.

As the brain size affects volume and cortical thickness calculations (Luders et al., 2006), the ICV was used to provide global scaling for volumes of the total brain and subcortical structures. To verify the ICV results, the atlas scaling factor (ASF) was calculated from the linear transformation matrix produced by FLIRT. ASF is a volume scaling factor used for scaling a subject's skull-stripped brain to a template.

Subcortical structures assessment

FreeSurfer only allows for a vertex-wise analysis of cortical structures; therefore, in order to compare the subcortical structures their volumes were estimated from a processing stage of FreeSurfer. Volumes of subcortical structures were estimated from the volumes of the segmented subcortical structures (in mm³). In order to correct for differences in head size, the volumes were normalized by the individual ICV.

Statistical analysis

The global brain measurements and volumes of subcortical structures were tested for between-group differences, using a univariate test with gender and group as fixed factors, age as a covariate. A full factorial model was used, with group difference as a contrast. The analysis was also repeated for female subjects only, as, due to the nature of the disease, there were fewer male patients, and therefore fewer male controls, making the estimation of gender effect difficult.

2.3.3.2 FSL-VBM

FSL-VBM is a fully automated whole brain morphometric technique that detects regional differences in tissue types composition on a voxel by voxel basis. It provides an automated whole-brain analysis of estimated grey matter concentration around a given voxel (Ashburner and Friston, 2001).

The template was created from a subset of the study subjects matched with respect to age and gender of the whole group to avoid bias during normalisation. The images were normalised using a non-linear spatial transformation (Good et al., 2001).

Grey matter preprocessing

Whole-brain differences in the topographic distribution of grey matter between RA patients and healthy controls were analysed using a FSL-VBM software, a voxel-based mor-

phometry style analysis (Good et al., 2001; Ashburner and Friston, 2000) carried out with FSL tools (Smith et al., 2004). First, structural images were brain-extracted using BET (Smith, 2002). Next, tissue-type segmentation was carried out using FAST4 (Zhang et al., 2001). The resulting grey matter partial volume images were then aligned to the MNI152 standard space using the affine registration tool FLIRT (Jenkinson and Smith, 2001; Jenkinson et al., 2002), followed by non-linear registration using FNIRT (Andersson et al., a,b, 2008), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). The resulting images were averaged to create a study-specific template, to which the native grey matter images were non-linearly re-registered. The study-specific grey matter template was created from a subgroup of 25 patients' and all 25 controls' grey matter segmented images (equal number of subjects from each group). The registered partial volume images were then modulated (to correct for local expansion or contraction) by dividing by the Jacobian of the warp field. The modulated segmented images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. Finally, voxel-wise GLM was applied using a permutation-based non-parametric testing, correcting for multiple comparisons across space.

Group differences

Differences in the distribution of grey matter between patients and healthy volunteers were examined using permutation-based non-parametric inference testing within the framework of the GLM (Nichols and Holmes, 2002). The first two regressors in the model represented patients and controls groups mean. The four additional regressors of no interest represented patients' demeaned age and gender. This allowed for a between-group comparison controlling for the effect of age and gender. Two contrasts were set for differences between patients versus controls and vice versa. A voxel-wise statistical map was created, that identified grey matter differences between the groups. Results were considered significant at $p < 0.05$ (5000 permutations, initial cluster-forming thresholding at $p - uncorrected = 0.05$), fully corrected for multiple comparisons.

Effect of disease duration and pain intensity

To test for the effect disease duration and an effect of daily pain intensity, two separate analyses were performed within the patient group. In the GLM (Nichols and Holmes, 2002), the first regressor was used to model group mean, the second to model demeaned age, the third to model demeaned gender, and fourth demeaned disease duration. In the second analysis, the fourth regressor represented demeaned daily pain intensity at the baseline visit. Results were considered significant at $p < 0.05$ (5000 permutations, initial cluster-forming thresholding at $p - \text{uncorrected} = 0.05$), fully corrected for multiple comparisons.

2.3.4 Analysis of clinical and psychophysical data

The clinical and psychophysical data were analysed using a standard statistical software package SPSS version 16 for Mac OS X (SPSS Inc., Chicago, USA). The standard statistical tests available in the SPSS were used. The analyses were described in detail in the results chapters. As pain ratings were ordinal variables and other variables were mostly non-normally distributed, non-parametric tests were used. All significance tests were two tailed and conducted at the $p < 0.05$ significance level.

2.3.4.1 Participants characteristics

Descriptive analyses were used to assess all the data. The mean and standard deviation (SD) were given for normally distributed variables and median and interquartile range (IQR) for ordinal or non-normally distributed variables.

2.3.4.2 Between-group differences

The Fisher's exact test for small sample size was used to test for differences in categorical data and the Mann–Whitney U test for differences in continuous data.

2.3.4.3 Effect of treatment on clinical and psychological variables

The Wilcoxon signed-rank test was used to test whether there were statistically significant differences in clinical, psychological, and psychophysical scores before and after the treatment. Moreover, differences between the values at the baseline and values at the subsequent visits were calculated.

Correlation analysis

To investigate the interactions between the variables, exploratory correlations were calculated between clinical, psychological, and psychophysical variables. As pain ratings were ordinal variables, and other variables were either ordinal or non-normally distributed, the Spearman's Rank Order Correlation ρ was used.

2.3.4.4 Factor analysis

Factor analysis was performed to investigate the underlying dimensions in the clinical, psychological and psychophysical variables and to analyse how the variables were related to each other. In this method, there is no specification of either dependent variables, independent variables, or causality. This is useful, particularly in this study, to investigate the interdependence of changes in observed variables, as the causality of changes in inflammation, depression, pain and disease activity is not straightforward.

The observed variables were modelled as linear combinations of the factors plus an error. This method makes it possible to identify groups of the inter-related variables and also to reduce the measured variables to a few factors, which may be used in the GLM for fMRI data analysis. The disadvantage of factor analysis is that there is more than one possible interpretation of the results and no information about causality. In this study, the factors were identified using the Principal Component Analysis. A Varimax rotation method with Kaiser Normalisation was used to minimise the number of variables loading on one factor and to keep the factor orthogonal.

Chapter 3

PAIN PROCESSING IN RHEUMATOID ARTHRITIS

3.1 Introduction

There have been several neuroimaging studies comparing evoked pain processing in chronic pain patients and healthy controls. It has been demonstrated that if the perceived pain intensity is the same, then the pain-related brain activation is largely similar in patients and in controls; however, if the same stimulus intensity is used, patients show more extensive activation, which suggests an augmentation of pain (Giesecke et al., 2004; Gracely et al., 2002; Jensen et al., 2009).

There are only a few neuroimaging studies on arthritic pain, all of them using PET. Kulkarni and colleagues (Kulkarni et al., 2007) have found that the response to heat-evoked pain in osteoarthritis patients results in a similar brain activation pattern as the one described in healthy controls. In RA, Jones and Derbyshire (Jones and Derbyshire, 1997) described a reduced activation in response to heat pain in patients in comparison to healthy controls.

3.2 Aims and hypotheses

The aim of this chapter was to compare the brain activation in response to two types of noxious stimuli, mechanical and thermal, in RA patients. We were also interested in the clinical and psychological factors that affect pain processing. As pain processing in RA has not been extensively studied, we wanted to investigate whether there are any dif-

ferences in evoked-pain processing between RA patients and age- and gender-matched healthy control subjects.

3.3 Methods

3.3.1 Participants

Data from the baseline visit for RA patients PAT_{BL} and healthy controls CON_{BL} were used for the analyses in this chapter.

3.3.2 Procedures

Pre-scanning assessment, thresholding, and scanning protocol used at the baseline were described in detail in the Methods chapter subsection 2.2.5.

3.3.3 Analysis of clinical, psychological and psychophysical data

As most of the data were not normally distributed we used non-parametric tests available in SPSS such as the Mann–Whitney U test.

3.3.3.1 Interactions between the measured variables in the patient group

The interactions between the measured variables were analysed using the Spearman's Rank Correlation Coefficient, ρ .

As several variables correlated with each other, a factor analysis was used to characterise the patterns of relationships, i.e., underlying dimensions in the measured clinical, psychological and psychophysical variables. The following data were entered into the factor analysis: the disease activity score (DAS28) and all its components (tender and swollen joint count, subjective rating of general health, and levels of inflammatory mark-

ers), average daily pain intensity, duration of joint stiffness, strength of the pressure stimuli, temperature, pain ratings for pressure and heat pain, depression and catastrophising scores.

3.3.3.2 Effect of depression in the patient group

As clinically depressed patients were not excluded from this study, the effect of depression was investigated.

Patients were divided into three categories: those with current depression, those with past history of depression, and those who were never diagnosed with depression. We have used this division because Himmerich and colleagues (Himmerich et al., 2008) have demonstrated that TNF and TNF-receptor levels are different between these three groups, i.e., the highest in people (not RA patients) with acute depression, and lowest in people who were never diagnosed with depression. TNF levels are likely to affect the clinical and psychophysical measures in this study. Moreover, Zautra and colleagues (Zautra et al., 2007) found that RA patients with several episodes of major depression experienced more pain than patients with one episode of depression or with no depressive episodes in the past.

We used the Mann–Whitney U test to compare the clinical, psychological, and psychophysical variables between patients who were depressed at the time of the study, and patients who were never diagnosed with depression, i.e., the two extreme groups. We have compared only two groups to simplify the analysis and interpretation of the results.

3.3.3.3 Group difference in psychological and psychophysical data

The psychological and psychophysical data between the RA patients and controls were compared using the Mann–Whitney U test.

The data from the pressure condition and the stimulation-matched heat condition were analysed in the subset of 23 patient-control pairs as the controls received stimuli of the same intensity as patients of the same gender and similar age. The psychophysi-

cal data for the perception-matched heat condition were analysed in the matched subset of participants as well as in the full dataset of 62 participants (36 patients and 26 controls). Not all the patients had matching controls due to difficulties in recruiting healthy, middle-aged volunteers. Three controls were not matched to patients as they were of the opposite gender, or the age difference between them and the patient they could be matched to was over ten years.

The rationale for the patient-control matching was that both age and gender affect pain, and a stimulus that was painful for an old woman might not be painful for a young man, and a stimulus that was painful for young man might be intolerable for an old woman. The paired t-test was not appropriate as the patients and controls, although paired for age and gender, are still varied in many other measures. The Mann–Whitney U test was used for between-group comparisons, although it did not account for the pairing. More advanced statistical methods such as multi-factor analysis of variance, could not be used because of small sample size.

3.3.4 Analysis of imaging data

3.3.4.1 Mean effect analysis and between-group differences

The mean group effect was investigated using a single group average, i.e., a one-sample t-test within the GLM.

To qualitatively compare the between-group differences in the brain activation pattern the statistical maps of mean activation, in the patient and control group, were overlaid.

A group difference between patients and controls was also statistically analysed using a two-sample unpaired t-test. The analyses were performed for the pressure- and heat-evoked pain, separately. For the pressure condition and for the stimulation-matched heat condition, the comparison between patients and controls was done only in the matched subset of participants. The comparison of the perception-matched heat was done in the full dataset and in the matched subset.

3.3.4.2 Factors modulating pain perception

To explain pain-related brain activation in the patient group, factor scores from the factor analysis were entered into the GLM as regressors of interest.

Factor analysis makes it possible to use in the model information from all the measured variables without a need to arbitrarily choose only a few variables. As it allows us to describe the observed variables in terms of a smaller number of variables called factors, it reduces the number of covariates entered into the GLM.

The first regressor in the model represented the group mean and the remaining regressors corresponded to the values of the factor scores. Each patient's loadings on each factor were entered into the GLM in order to better explain the pain-evoked brain activation. Contrasts were set for the activation that covaried positively and negatively with each factor. The analysis was performed for the pressure- and heat-evoked activation, separately.

3.3.4.3 Effect of depression on pain processing in the patient group

A two-sample unpaired t-test was used to analyse a difference between currently depressed patients and patients who were never diagnosed with depression.

3.3.4.4 Differences in response to pressure and heat pain in the patient group

In patient group, the brain activation in response to pressure and activation in response to heat pain was qualitatively compared by overlaying the mean activation maps in response to pressure and heat.

A statistical analysis was also performed between the pressure and heat-evoked activation for each patient using a two-sample paired t-test.

3.4 Results

3.4.1 Participants characteristics

From 38 patients recruited into the study; data of one patient was excluded because of motion artefacts and one patient was re-diagnosed with polymyalgia rheumatica after the baseline visit, leaving data from 36 patients for the analyses in this chapter. The median age in the patient group was 57.0 years (IQR 22). The ratio of female to male patients was 27 to 9, which corresponds to the gender ratio in the general population of RA patients. The clinical characteristics of the RA group at the baseline are summarised in Table 3.1.

29 healthy, pain-free, age- and gender-matched volunteers were recruited into the study as a control group. One person was excluded due to a probable joint disease, and two subjects were claustrophobic; therefore, data for 26 controls were used for the analyses. The mean age in the control group was 59.0 years (IQR 16); there were 18 female and 8 male subjects.

Groups were well matched with respect to age; the Mann–Whitney test (2-tailed) $p = 0.612$ and gender, the Fisher’s exact test $p = 0.774$.

There were 23 matched patient-control pairs. The median age in the patient group was 54.0 (IQR 22.0), and in the control group the median age was 59.0 (IQR 16.0), but the difference was not statistically significant (the Mann–Whitney U test $p = 0.644$). There were 17 women and six men in the control group.

Table 3.1: Summary of clinical data of the RA patients

Variable		Value
N		36
Female-to-male ratio		27/9
Age, years	median (IQR)	57.0 (22)
Disease duration, years	median (IQR)	15.0 (11.8)
Disease activity	mean (SD)	6.05 (0.9)
Tender joint count	median (IQR)	11.5 (7)
Swollen joint count	median (IQR)	11.0 (7)
Erythrocyte sedimentation rate, $\frac{\text{mm}}{\text{h}}$	median (IQR)	30.0 (29.0)
C-reactive protein, $\frac{\text{mg}}{\text{l}}$	median (IQR)	16.0 (26.0)
Duration of joint stiffness, minutes	median (IQR)	60.0 (68)
Daily pain intensity	median (IQR)	6.5 (2.5)

Co-morbidities in the patient group

This was an observational study, therefore, patients were not excluded if their other medical conditions were unlikely to affect the results of this study or were associated with RA or chronic pain, e.g., depression. It has been suggested that TNF may be involved in the pathogenesis of depression, and diabetes, hypertension, osteoporosis are common comorbidities in depression (Himmerich et al., 2008). Four patients suffered from osteoarthritis secondary to RA; one patient had a history of carpal tunnel syndrome that resolved spontaneously; five patients had hypertension; two were diagnosed with diabetes mellitus type 2; and two had asthma. The conditions were mild and well controlled by medication, and therefore were unlikely to affect the results of the study. The diabetic patients did not present any signs of peripheral neuropathy.

Eleven out of 36 patients were at some point in their life diagnosed with depression, out of whom six were clinically depressed at the time of this study. There was no difference between the currently depressed and non-depressed group in clinical, psychological and psychobehavioural measures. However, currently depressed patients in comparison to never depressed patients had a significantly higher (the Mann–Whitney test) number of tender joints ($p = 0.046$), a higher ratio of tender to swollen joints ($p = 0.002$), and a higher depression score ($p = 0.007$). There was no difference between depressed and non-depressed patients in pressure strength, temperature, daily pain intensity, disease activity, swollen joint count, ESR or catastrophising scores.

Eight patients reported other pain conditions: five patients had headaches or migraine, and three suffered recurrent back pain. The intensity of the other pain was mild, and pain attacks were not frequent; therefore, those patients were included in the study. The subsequent analysis confirmed that there were no differences in clinical or psychological measures between the patients with and without other pain complaints.

Medication in the patient group

As this was an observational study, patients were allowed to continue prescribed medication, including disease-modifying anti-rheumatic drugs (DMARDs) at stable doses.

Twenty seven patients were taking DMARDs other than anti-TNF during the study: Methotrexate ($n = 13$), Leflunomide ($n = 8$), Hydroxychloroquine ($n = 9$), Cyclosporine ($n = 2$), Azathioprine ($n = 1$). Nine patients were taking steroids. Nineteen patients were taking single DMARD, five two DMARDs, and three patients were taking three DMARDs. Thirty three patients were taking pain-killers, and twenty one of them were able to refrain from pain-killers 24 hours before the scanning session. Six patients were taking antidepressants: Amitriptyline ($n = 4$) and Citalopram ($n = 2$).

3.4.2 Psychological scores

The median depression and catastrophising scores were higher in patients than in controls (Table 3.2 and Figure 5.5). Also the severity of depressive symptoms was higher in the patient group (Table 3.3).

There was a high correlation between depression and catastrophising scores in the patient group, Spearman's (2-tailed) $\rho = 0.758, p < 0.0005$, and in the control group $\rho = 0.416, p = 0.035$. In the patient group, the psychological scores did not correlate with the disease activity or inflammatory markers.

All subjects, patients and controls, scored over 26 on the Mini Mental State Examination and did not show any signs of cognitive impairment.

Table 3.2: Depression and catastrophising scores for patients and controls

Variable	Patients	Controls	P-value
Depression score	12.0 (11.0)	4.0 (6)	< 0.0005
Catastrophising score	15.0 (20.8)	5.0 (9)	< 0.0005

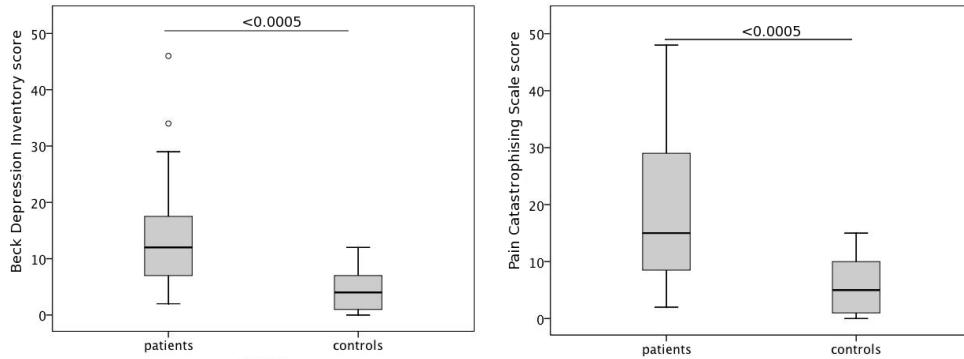
Median value and interquartile range for Beck Depression Inventory score and Pain Catastrophising Scale score for each group, and the p-value for the Mann-Whitney U test (2-tailed) between the groups.

Table 3.3: Severity of depressive symptoms in patients and controls

Depression score	<i>no depression</i>	<i>mild depression</i>	<i>moderate depression</i>	<i>severe depression</i>
	< 9	10-18	19-29	> 30
Patients	14	16	4	2
Controls	22	4	0	0

The severity of depressive symptoms assessed with the Beck Depression Inventory in the patient and control group.

Fig. 3.1: Depression and catastrophising scores in patients and controls



Results, absolute values, of the Beck Depression Inventory (BDI) and Pain Catastrophising Scale (PCS) scores in patients (n=36) and controls (n=26). Median values are presented within the 25th and 75th interquartile box, non-outlier maxima and minima (whiskers). o - an outlier $< 3IQR$ above the 75th quartile.

3.4.3 Psychophysical data

3.4.3.1 Pressure stimulation

In the patient group, the pressure intensity required to evoke moderate pain was 4 out of 6 (IQR 2), and it resulted in a median post-scanning pain rating of 5 out of 10 on the NRS (IQR 2.0) (Figure 3.2).

In the control group, volunteers received the pressure stimuli of the same pressure as patients to whom they were matched with respect to age and gender. There were 23 matched patient-control pairs. Mechanical stimuli at an equal pressure as given in the patient group, were not perceived as painful by healthy controls, and the median pain rating was 0 (IQR 0.5) (Figure 3.2 and Table 3.4).

Table 3.4: Summary of psychophysical measures in patients and controls

Variable	Patients	Controls	P-value
Pressure pain rating, matched subjects	5.0 (2.0)	0 (0.5)	< 0.0005
Stimulation-matched heat pain rating, matched subjects	5.5 (1.5)	4.5 (2.0)	0.021
Perception-matched heat pain rating, matched subjects	5.5 (1.5)	6.0 (0.5)	0.262
Perception-matched heat pain rating, all subjects	5.5 (1.0)	6.0 (1.0)	0.037
Temperature, matched subjects	53.0 (4.0)	55.0 (3.8)	0.031
Temperature, all subjects	53.0 (4.5)	55.0 (3.0)	0.036

Psychophysical measures in the patient and control group. Median and interquartile range for each group, and significance of Mann-Whitney U test (2-tailed) between the groups.

Table 3.5: Pain ratings for the perception-matched heat pain subdivided by gender

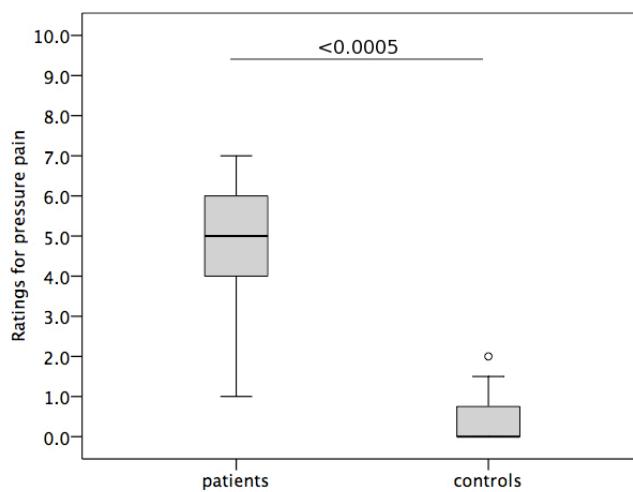
Perception-matched heat pain rating	Patients	Controls	P-value
Men	5.0 (1.0)	6.3 (1.1)	0.066
Women	5.5 (1.0)	6.0 (0.5)	0.184

Pain ratings for the perception-matched heat pain in all subjects subdivided by gender. Median values and interquartile range for each group, and significance of Mann-Whitney U test (2-tailed) between the patient and control group.

3.4.3.2 Heat stimulation

In the patient group, the median temperature necessary to evoke moderate pain was 53° Celsius (IQR 4.5), and the median post-scanning pain rating was 5.5 (IQR 1.0).

Fig. 3.2: Pain ratings for pressure pain in patients and controls



Results, absolute values, pain ratings of pressure-evoked pain in matched patients and controls. Median values are presented within the 25th and 75th interquartile box, non-outlier maxima and minima (whiskers). o - an outlier < 3IQR above the 75th quartile.

In the control group, two heat intensities were used: stimulation-matched and perception-matched. During the stimulation-matched condition, controls received a temperature that was perceived by a patient of the same gender, and similar age as moderately painful, i.e., 5–6 out of 10 on the NRS. During the perception-matched condition, controls received temperature that was perceived by them as moderately painful.

The stimulation-matched heat in the 23 matched controls evoked a median pain rating of 4.5 out of 10 (IQR 2.0) (Figure 3.3). Although the same temperature was applied to an age- and gender-matched control subject, controls rated the stimuli lower than patients; Mann–Whitney test $p = 0.021$ (Table 3.4).

During the perception-matched condition in the 23 matched controls, the mean temperature of 55° Celsius (IQR 3.8) was chosen by controls to evoke moderate pain (Figure 3.5). The median pain rating given after the scanning session was 6 out of 10 (IQR 0.5) (Figure 3.4). The difference between patients and matched controls for the ratings of the perception-matched heat was not statistically significant; the Mann–Whitney test $p = 0.262$. However, when all the patients ($n=36$) were compared with all the controls ($n=26$) the difference in pain ratings was significant (Table 3.4). This is probably due to gender effect as the differences were not significant for participants of the same gender (Table 3.5).

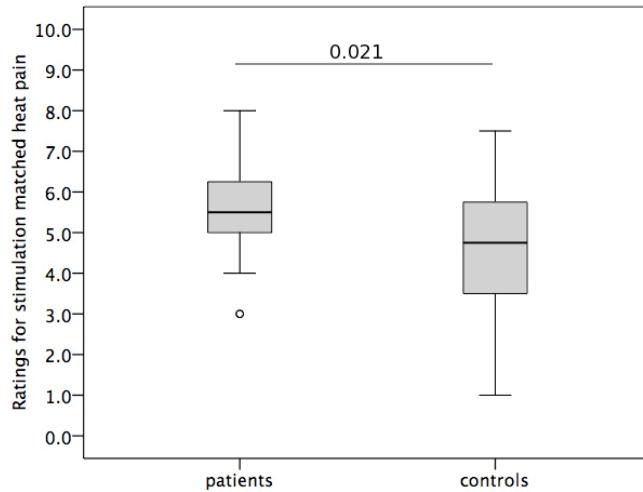
The temperature required to evoke moderate pain was lower in patients than in matching controls; the Mann–Whitney test $p = 0.031$. This effect was still present when data for all the patients and controls data were analysed (Table 3.4).

3.4.3.3 Clinical and psychological factors moderating pain

Patients

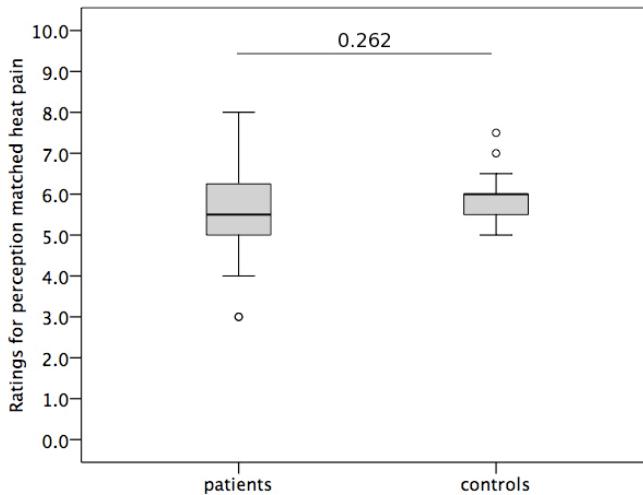
In the patient group, the daily pain intensity correlated positively with the disease activity and with the duration of joint stiffness. The reported daily pain intensity was higher in women than in men; the Mann–Whitney test (2-tailed) $p = 0.012$. The intensity of daily pain did not correlate with swollen or tender joint count, inflammatory markers, depression or catastrophising scores.

Fig. 3.3: Pain ratings for the stimulation-matched heat condition



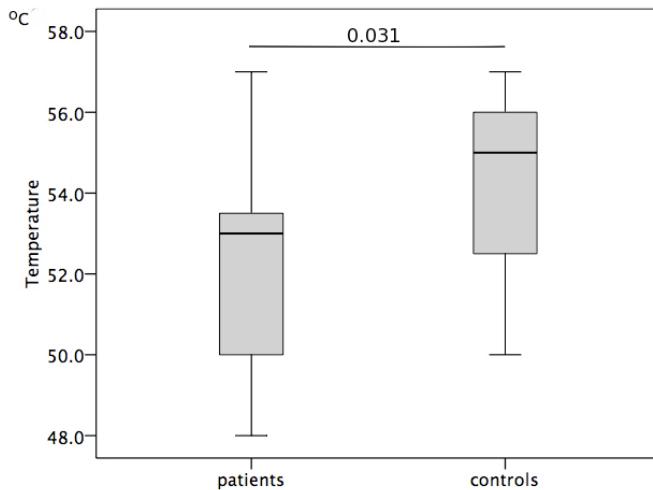
Results, absolute values of pain ratings for stimulation-matched heat condition in matched patients and controls. Median values of the pain ratings are presented within the 25th and 75th interquartile box, non-outlier maxima and minima (whiskers). o - an outlier $< 3IQR$ above the 75th quartile.

Fig. 3.4: Pain ratings for the perception-matched heat condition



Results, absolute values of pain ratings for perception-matched heat condition in matched patients and controls. Median values of the pain ratings are presented within the 25th and 75th interquartile box, non-outlier maxima and minima (whiskers). o - an outlier $< 3IQR$ above the 75th quartile.

Fig. 3.5: Temperature evoking moderate pain in patients and controls



Results, absolute values of temperature evoking moderate pain in matched patients and controls. Median values of temperatures are presented within the 25th and 75th interquartile box, non-outlier maxima and minima (whiskers).

Table 3.6: Correlations between clinical, psychological and psychophysical measures in the patient group

Variable	Correlation											
	1	2	3	4	5	6	7	8	9	10	11	12
1. Disease activity	-											
2. Tender joint count	0.62	-										
3. Swollen joint count	0.53	0.22	-									
4. Erythrocyte sedimentation rate	0.69	0.09	0.16	-								
5. Daily pain	0.34	0.08	0.14	0.23	-							
6. Joint stiffness	0.13	0.23	-0.01	-0.06	0.43	-						
7. Pressure pain rating	0.11	0.21	0.17	-0.14	-0.06	0.05	-					
8. Heat pain rating	0.46	0.33	0.16	0.26	0.23	0.13	0.4	-				
9. Pressure strength	-0.05	-0.08	-0.04	0.15	-0.22	-0.15	-0.07	0.003	-			
10. Temperature	-0.23	-0.12	-0.26	-0.03	-0.38	-0.25	-0.26	-0.04	0.34	-		
11. Catastrophising score	0.05	-0.01	0.19	-0.06	0.24	0.27	0.02	0.08	-0.22	-0.30	-	
12. Depression score	0.09	0.10	-0.04	0.03	0.32	0.28	0.06	0.07	-0.12	-0.18	0.76	-

Spearman's ρ correlations between the clinical, psychological and psychophysical variables in the patient group. Significance at the $p < 0.05$ level (corrected for multiple comparisons using Bonferroni correction $0.05/12 = 0.004$) marked in bold font.

In this study, pain ratings were calibrated to 5–6 on the NRS; therefore the strength of stimuli required to evoke moderate pain was more informative than pain ratings. Strength of both types of stimuli, pressure strength and temperature, correlated with each

other, but they did not correlate with patients' disease activity, inflammatory markers, depression or catastrophising scores.

The pressure strength did not correlate with daily pain intensity, and did not differ between men and women. However, it was higher in the group that did not take pain-killers on the day of the scan – median 4 (IQR 2), than those who took pain-killers – median 3 (IQR 1.0); the Mann–Whitney test (2-tailed) $p = 0.008$. This means that the patients who were in so much pain that they could not refrain from pain-killers still required weaker stimuli to give a pain rating of 5–6 on the NRS. This would suggest that these patients perceived the pressure stimuli as painful, despite taking analgesics.

The temperature perceived as moderately painful correlated negatively with daily pain, and was lower in women than in men; the Mann–Whitney test (2-tailed) $p = 0.002$. The temperature did not differ between patients who did and did not take pain-killers on the day of the scan.

George and colleagues (George and Hirsh, 2009) have demonstrated that catastrophising and gender are the main predictors of clinical pain; therefore, the correlation analyses were repeated in female and male patients separately. In women, there was a strong negative correlation between the catastrophising score and temperature perceived as moderately painful $\rho = -0.524, p = 0.005$, there was also a trend for a negative correlation between depression scores and temperature ($\rho = -0.332, p = 0.091$), and between depression scores and daily pain intensity ($\rho = 0.356, p = 0.068$). In men, there was a trend for a negative correlation between catastrophising scores and temperature ($\rho = -0.588, p = 0.096$), and a trend for correlation between catastrophising score and daily pain intensity ($\rho = 0.603, p = 0.086$). There was no difference in depression and catastrophising scores between male and female RA patients; the Mann–Whitney U test $p=0.615$ and $p=0.233$, respectively.

Controls

In the control group, the temperature rated as moderately painful (perception-matched condition) did not correlate with age, depression or catastrophising scores, and did not differ between men and women.

3.4.3.4 Factor analysis in the patient group

The measured variables entered into the factor analysis were separated into five main components, each with an eigenvalue larger than 1 (Figure 3.6). These factors explained 75.5% of the total variance in the measured variables. The Kaiser-Meyer-Olkin Measure of Sampling Adequacy was 0.53; therefore it was appropriate to carry out a factor analysis. The closer the Kaiser-Meyer-Olkin Measure is to 1 the more likely it is that the pattern of correlations is compact and that the factor analysis will give reliable factors. Values above 0.5 are acceptable.

The Bartlett's Test of Sphericity was significant at $p < 0.0005$; therefore the null hypothesis that the variables in the correlation matrix are uncorrelated could be rejected. The Bartlett's Test of Sphericity tests whether there are any relationships between the variables, i.e., that some of variables are correlated.

Inflammatory markers, ESR and CRP, loaded positively, and pain ratings for pressure pain loaded negatively on the first factor, which had an eigenvalue of 4.09 and explained 19.8% of the variance.

The second factor had an eigenvalue of 2.7 and explained 16.1% of the variance. The second factor represented depression and catastrophising scores, as well as the duration of joint stiffness.

The disease activity in 28 joints, the tender joint count, and heat pain ratings were represented by the third factor. The third factor had an eigenvalue of 1.7 and explained 15.9% of the variance.

The subjective rating of general health and the daily pain intensity loaded mainly on the fourth factor, together with negative loadings for pressure strength and temperature. This would suggest that the reported daily pain intensity was associated with the general

health and patients' perception of disease activity, rather than the degree of inflammation. The fourth factor had an eigenvalue of 1.1 and explained 14.3% of the variance.

Finally, the swollen joint count, which reflects the amount of inflamed synovial tissue (Naredo et al., 2005), loaded on the fifth factor, which had an eigenvalue of 1.0 and explained 9.3% of the variance.

Therefore, the first factor represented the inflammatory domain; the second factor represented the psychological domain; the third factor reflected the objective clinical status; the fourth factor represented patient's perception of clinical status, and the fifth factor represented the swollen joint count.

Fig. 3.6: Factor loadings from the factor analysis

	Component				
	1	2	3	4	5
CRP	.879	.007	-.075	.105	.175
ESR	.847	-.053	.251	-.011	.125
Rating for pressure	-.686	.134	.436	.247	.177
Depression	-.028	.879	.181	.153	.028
Catastrophising	-.049	.806	-.083	.220	.342
Joint stiffness	.023	.718	.173	.190	-.212
Tender joint count	.014	.200	.826	-.115	.050
Rating for heat	-.073	.010	.772	.280	-.033
Disease activity	.548	.104	.718	.095	.340
Pressure strength	.304	-.101	.015	-.767	-.003
Temperature	-.047	-.312	-.057	-.643	-.316
General health	.422	.241	.277	.622	-.038
Daily pain intensity	.456	.272	.124	.573	-.041
Swollen joint count	.160	.018	.111	.077	.919

Rotated component matrix.

3.4.3.5 Effect on depression in the patient group

Six out of 36 patients were depressed at the time of the study, and five were diagnosed with depression in the past. Currently depressed patients in comparison to patients who were never diagnosed with depression (the Mann–Whitney test, 2-tailed) had higher depression scores ($p = 0.007$), higher tender joint count ($p = 0.046$), and higher ratio of tender joints to swollen joints ($p = 0.002$). There was no difference in age, disease duration, catastrophising scores, daily pain intensity, duration of joint stiffness, swollen joint count,

disease activity scores or inflammatory markers. There were relatively more men in the group that was not depressed, than in the depressed group, i.e., men to women ratio was 8:17 and 1:5, respectively. The sample size was too small for a statistical analysis.

3.4.4 Imaging results

3.4.4.1 Pressure-evoked activation

In the patient group ($n = 36$), pressure-evoked pain resulted in extensive brain activation in brain regions typically reported in pain imaging studies (Figure 3.7 A). In the control group ($n = 26$), pressure stimulation resulted in a less extensive brain activation (Figure 3.7 B). For a qualitative comparison an overlay is shown in Figure 3.7 C.

A statistical comparison of activation in the matched patients and controls (23 patients and 23 matched controls, a two-sample unpaired t-test), demonstrated more extensive activation in the patient group: bilaterally in the primary motor and the primary somatosensory cortices, the premotor cortices, the anterior, mid- and posterior cingulate cortices, the precuneus, the thalamus, the insular cortex and operculum, the parahippocampal gyri, the brainstem, and the cerebellum (Figure 3.9).

3.4.4.2 Heat-evoked activation

In the patient group ($n = 36$), the moderately painful heat stimulation activated brain regions typically involved in pain processing (Figure 3.8 A).

The activation in response to heat pain was less extensive than activation in response to pressure, mainly in the secondary somatosensory cortex and the superior parietal gyri (an overlay in Figure 3.10). The statistical analysis, a two-sample paired t-test, demonstrated more activation in response to pressure than to heat, despite the fact that both stimuli were perceived by patients as moderately painful (Figure 3.11). The regions that were activated in response to pressure but not to heat included: bilaterally the primary motor and the primary somatosensory cortices, the superior parietal gyri, the supplemen-

tary motor areas, the premotor cortices, the medial prefrontal cortices, the midcingulate cortex, the secondary somatosensory cortices, the inferior parietal lobes, the insular cortices, the temporal lobes, the precuneus, the cerebellum, and the contralateral thalamus.

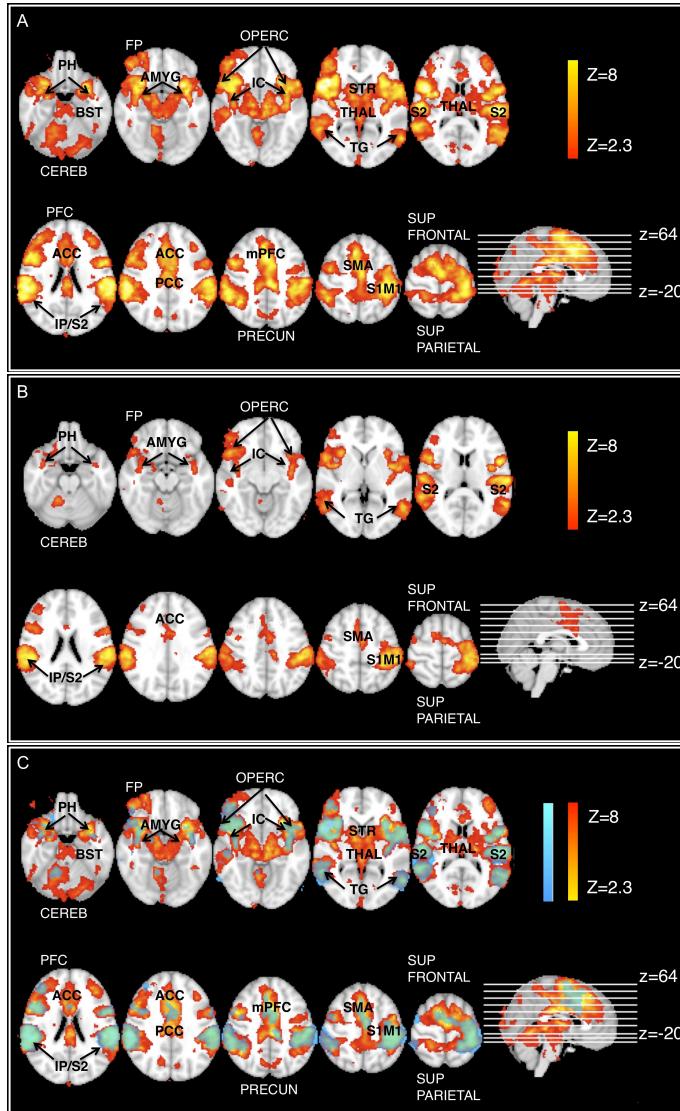
In the control group ($n = 26$), the perception-matched heat activated similar brain regions (Figure 3.8 B) as heat pain in the patient group (Figure 3.8 A); however, the activation was more extensive in the control group (an overlay in Figure 3.8 C). A statistical analysis between heat pain in the patient group ($n=36$) and the perception-matched condition in the control group ($n=26$) showed more activation in the control group in the contralateral posterior insular cortex and ipsilateral precuneus (Figure 3.12).

When only the matched patients ($n=23$) and controls ($n=23$) were analysed, there was more activation in the control group for the perception- as well as for the stimulation-matched condition. For the perception-matched condition, there was more activation in the control group in the contralateral primary motor, the contralateral primary and secondary somatosensory cortices, the contralateral insular cortex, and bilaterally in the superior parietal gyri, supplementary motor area, the anterior, mid- and posterior cingulate cortex, thalamus, striatum, and cerebellum (Figure 3.13). For the stimulation-matched comparison, controls showed more activation in the contralateral primary somatosensory cortex, the contralateral insular cortex, the operculum, and the bilateral thalamus and striatum (Figure 3.14).

3.4.4.3 Visual control task

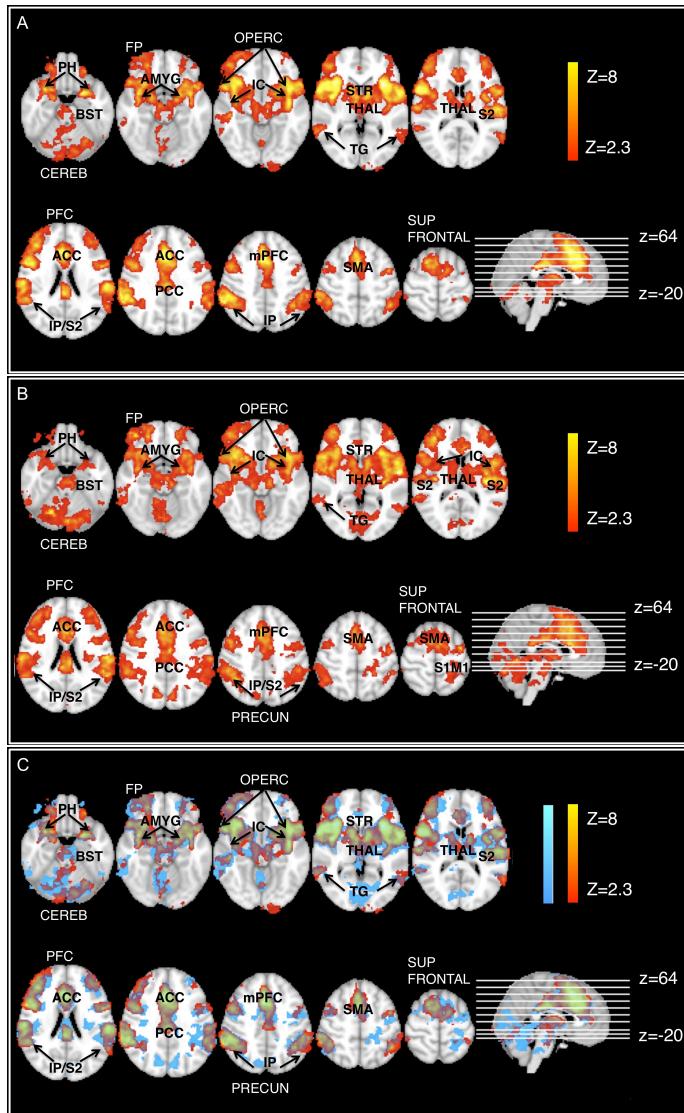
There was no difference between patients and controls in response to visual stimulation that was used as a control task. This suggests that the observed between-group differences are specifically due to altered pain processing in RA, and not due to generalised changes in the neuro-vascular response.

Fig. 3.7: Pressure evoked brain activation in patients and controls



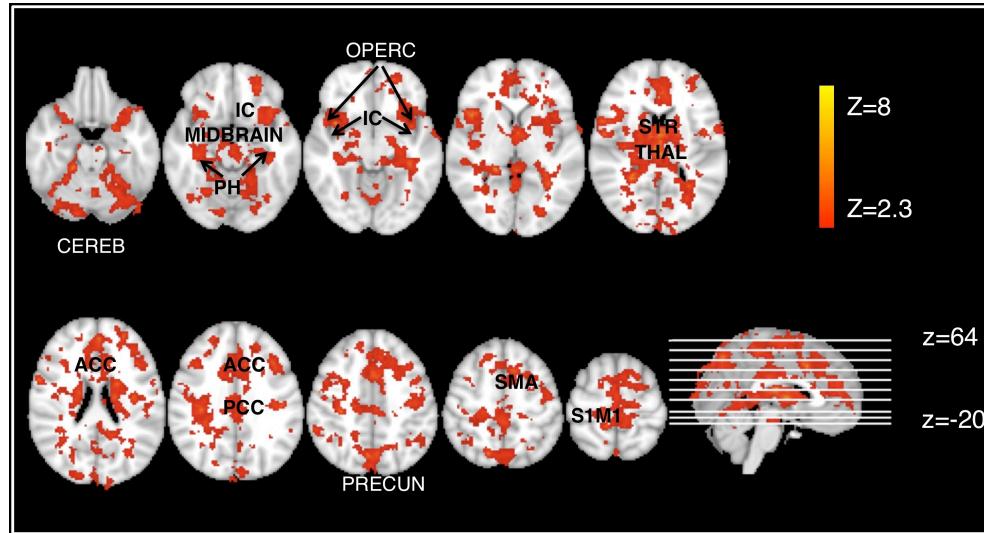
Brain activation in response to pressure stimulation. Mixed-effects analysis, $Z > 2.3, p < 0.05$. The mean group effect in the patient group (A), in the control group (B) and an overlay of both (C). (A) In the patient group the significant clusters were located bilaterally in the supplementary motor area (SMA), superior parietal gyri, medial prefrontal cortex (mPFC) and dorsolateral perfrontal cortex, anterior (ACC) and posterior cingulate (PCC) cortices, precuneus (PRECUN), secondary somatosensory cortex (S2) and inferior parietal lobe (IP), middle temporal gyrus (TG), insular cortex (IC) and operculum (OPERC), the thalamus (THAL), striatum (STR), parahippocampal gyri (PH), amygdalae (AMYG), brainstem (BST) and cerebellum (CEREB). There was also an activation in the contralateral primary motor (M1) and bilateral primary somatosensory (S1) cortices, and ipsilateral frontal pole (FP). (B) In the control group, the significant clusters were located in the contralateral primary somatosensory cortex (S1), contralateral primary motor cortex (M1); there was a bilateral activation in the supplementary motor area (SMA), anterior cingulate cortex (ACC), temporal cortex (TG), inferior parietal lobe (IP) and secondary somatosensory cortex (S2), insular cortex (IC), and operculum (OPERC), parahippocampal gyri (PH) bilaterally, and cerebellum (CEREB). (C) Overlay of activation in the patient group (red), in the control group (blue), and a conjunction (green).

Fig. 3.8: Heat evoked activation in patients and controls



Brain activation in response to heat stimulation. Mixed-effects analysis, $Z > 2.3, p < 0.05$. The mean group effect in the patient group (A), in the control group (B) and an overlay of both (C). (A) In the patient group the significant clusters were located bilaterally in the supplementary motor area (SMA), medial prefrontal cortex (mPFC) and dorsolateral perfrontal cortex, frontal pole (FP), anterior (ACC) and posterior cingulate (PCC) cortices, secondary somatosensory cortex (S2) and inferior parietal lobe (IP), temporal cortex (TG), insular cortex (IC) and central operculum (OPERC) bilaterally, thalamus (THAL) bilaterally, striatum (STR) bilaterally, parahippocampal gyri (PH), amygdala (AMYG), brainstem (BST) and cerebellum (CEREB). (B) The mean group effect in the control group for the perception-matched heat condition activated similar regions as heat stimulation in the patient group. (C) Overlay of activation in the patient group (red), control group (blue), and a conjunction (green).

Fig. 3.9: Group difference in brain activation in response to pressure stimulation



Group comparison of the pressure evoked brain activation, two-sample unpaired t-test, matched patients versus controls contrast ($PAT_{BL} > CON_{BL}$). Mixed-effects analysis, $Z > 2.3, p < 0.05$. Main clusters were located bilaterally in the primary motor (M1) and primary somatosensory (S1) cortex, supplementary motor area (SMA), anterior (ACC), mid- and posterior (PCC) cingulate cortex, precuneus (PRECUN), thalamus (THAL), striatum (STR), insular cortex bilaterally (IC), operculum bilaterally (OPERC), parahippocampal gyri (PH), midbrain, and cerebellum (CEREB).

3.4.4.4 Factor analysis in the patient group

Pressure pain

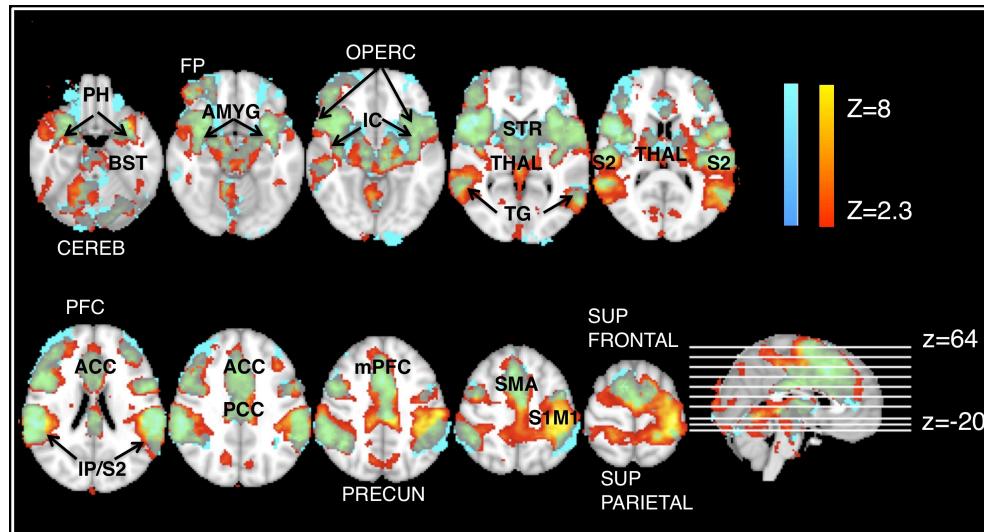
Pressure-evoked brain activation correlated only with the third factor representing the objective clinical status. A significant cluster of activation correlating with this factor was located in the ipsilateral anterior insular cortex (Figure 3.15).

Heat pain

The heat-evoked brain activation correlated with three of the five factors identified in the factor analysis.

There was a positive correlation between the first factor representing inflammation and the magnitude of activation in the contralateral primary and the secondary so-

Fig. 3.10: Brain activation in response to pressure and heat pain in the patient group, an overlay.



Overlay of mean effect map in response to pressure (red), heat (blue) in the patient group, and a conjunction of both (green).

matosensory cortices, the primary motor cortex, the supplementary motor area, and bilaterally in the anterior cingulate cortex (Figure 3.16).

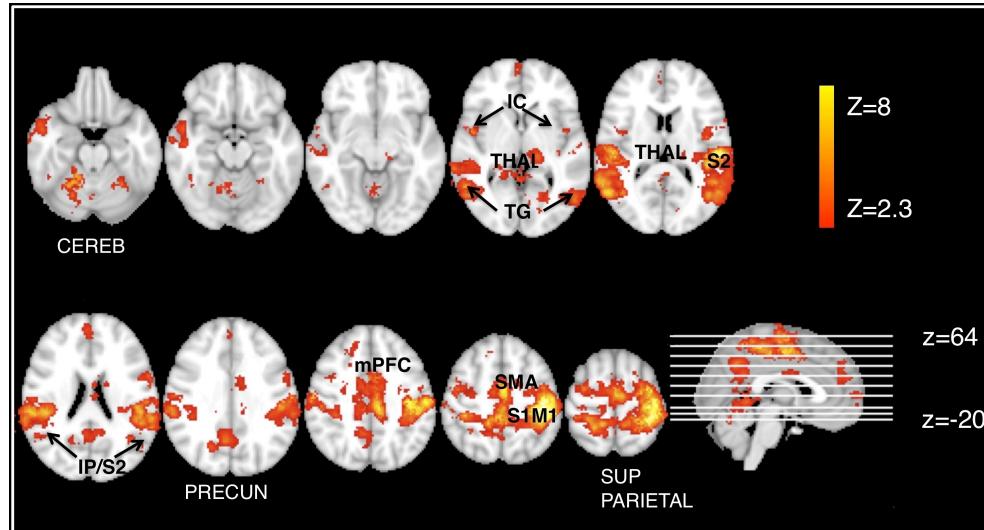
The second factor reflecting depression and catastrophising scores correlated positively with activation in the middle section of the cingulate cortex (Figure 3.17).

The fourth factor representing the subjective perception of clinical status negatively with activation in the thalamus bilaterally, and the putamen and posterior insular cortex ipsilaterally (Figure 3.18).

3.4.4.5 Effect of depression on pain processing in the patient group

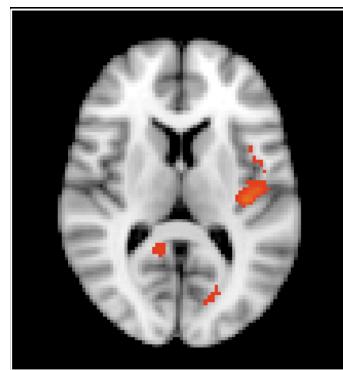
As there were only six patients in the depressed group a fixed-effects analysis was performed. The pressure-evoked brain activation was more extensive in the currently depressed group in comparison to patients who were never diagnosed with depression; *depressed > non-depressed* contrast, a two-sample unpaired t-test. There was more activation bilaterally in primary motor and primary somatosensory cortices, supplementary

Fig. 3.11: Difference in brain activation in response to pressure and heat pain in the patient group



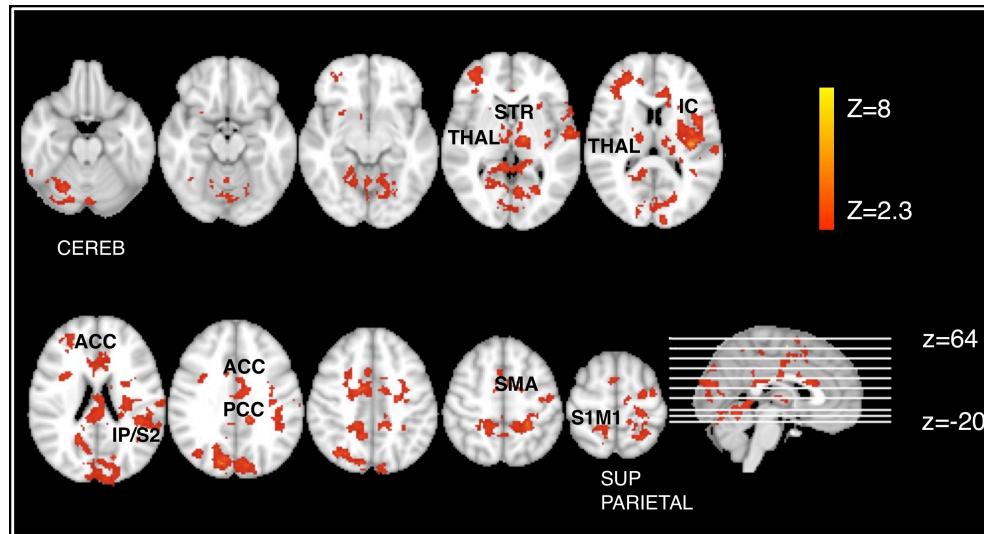
Paired comparison of the pressure and heat-evoked brain activation in the patient group, two-sample paired t-test, *pressure > heat* contrast. Mixed-effects analysis, $Z > 2.3, p < 0.05$. Significant clusters were located in the primary motor and the primary somatosensory (S1M1) cortices bilaterally, and bilaterally in the superior parietal gyri, the supplementary motor areas (SMA), the premotor cortices, the medial prefrontal cortices (mPFC), the midcingulate cortices, the secondary somatosensory cortices/inferior parietal lobes (IP/S2), the insular cortices (IC), the temporal cortices, the cerebellum, and in the contralateral thalamus (THAL).

Fig. 3.12: Group difference in brain activation in response to perception-matched heat stimulation



Group comparison of the perception-matched heat stimulation, two-sample unpaired t-test. Controls activate more strongly than patients ($CON_{BL} > PAT_{BL}$). All 62 subjects. Mixed-effects analysis. $Z > 2.3, p < 0.05$. Significant clusters were found in the contralateral posterior insular cortex, and ipsilateral pre-cuneus.

Fig. 3.13: Group difference in brain activation in response to perception-matched heat stimulation



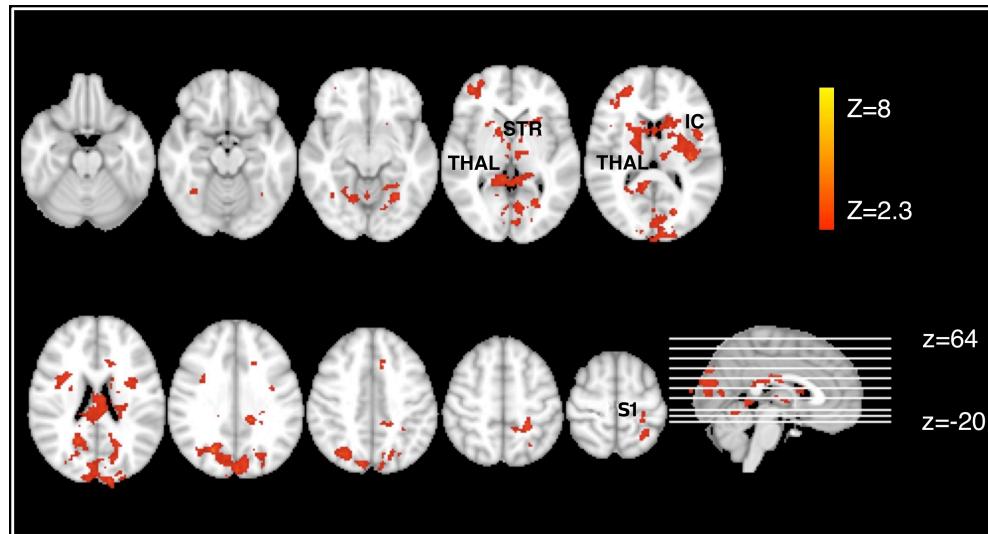
Group comparison of the perception-matched heat condition, two-sample unpaired t-test, matched controls versus patients contrast ($CON_{BL} > PAT_{BL}$). Mixed-effects analysis. $Z > 2.3, p < 0.05$. The significant clusters were located in the contralateral primary motor and primary somatosensory cortices (S1M1), the secondary somatosensory cortex and inferior parietal lobe (IP/S2), the contralateral insular cortex (IC) and operculum, and bilaterally in the superior parietal gyri, the supplementary motor areas (SMA), the anterior, mid- and posterior cingulate cortices (ACC and PCC), the thalamus (THAL), the striatum (STR), and cerebellum (CEREB).

motor area, frontal poles, anterior and midcingulate cortices, and the precuneus (Figure 3.19). No region was activated more in the non-depressed group than in the depressed group. There was no significant difference in pain ratings or stimuli strength between the depressed and non-depressed patients. There was no significant difference in the heat-evoked brain response.

3.5 Discussion

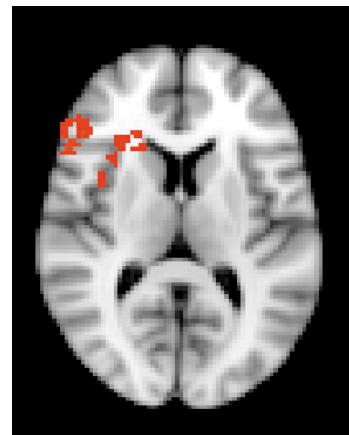
This is the first neuroimaging study comparing pain processing of mechanical and thermal painful stimuli in RA patients.

Fig. 3.14: Group difference in brain activation in response to stimulation-matched heat stimulation



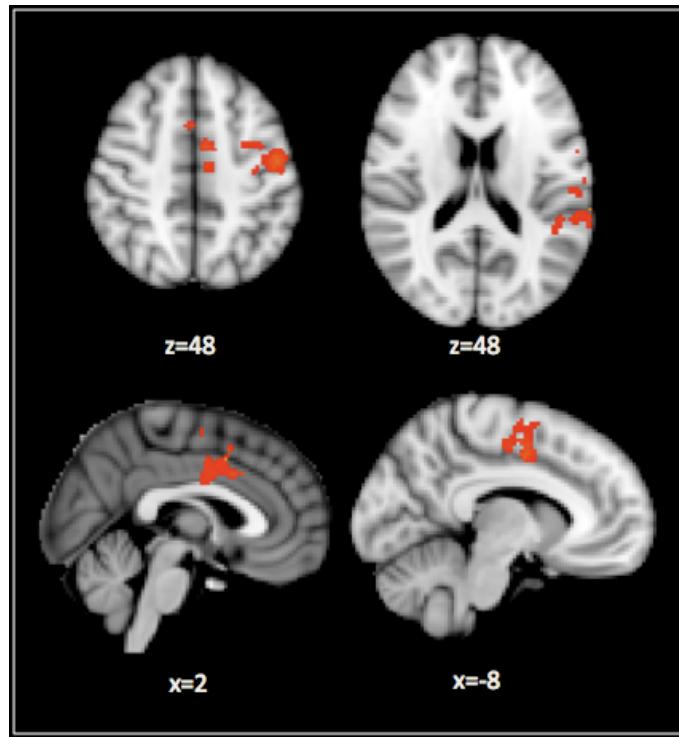
Group comparison of the stimulation-matched heat condition, two-sample unpaired t-test, matched controls versus patients contrast ($CON_{BL} > PAT_{BL}$). Mixed-effects analysis. $Z > 2.3, p < 0.05$. The significant clusters were located in the contralateral primary somatosensory cortex (S1), the contralateral insular cortex (IC) and operculum, the bilateral striatum, and the contralateral thalamus (THAL).

Fig. 3.15: Correlation between pressure-evoked brain activation and the third factor



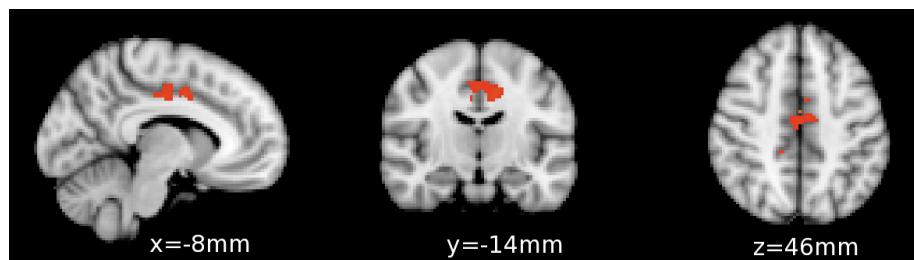
Positive correlation between the pressure-evoked brain activation and the third factor representing the objective clinical status. Mixed-effects analysis, $Z > 2.3, p < 0.05$. Significant cluster in the ipsilateral anterior insular cortex (cross-section at $z=10$ mm).

Fig. 3.16: Correlation between heat-evoked brain activation and the first factor



Positive correlation between the heat-evoked brain activation and the first factor representing the severity of inflammation. Mixed-effects analysis, $Z > 2.3$, $p < 0.05$. Significant clusters were located bilaterally in the middle section of the cingulate cortex, contralaterally in the supplementary motor area, the primary and secondary somatosensory cortices, and the primary motor cortex.

Fig. 3.17: Correlation between heat-evoked brain activation and the second factor



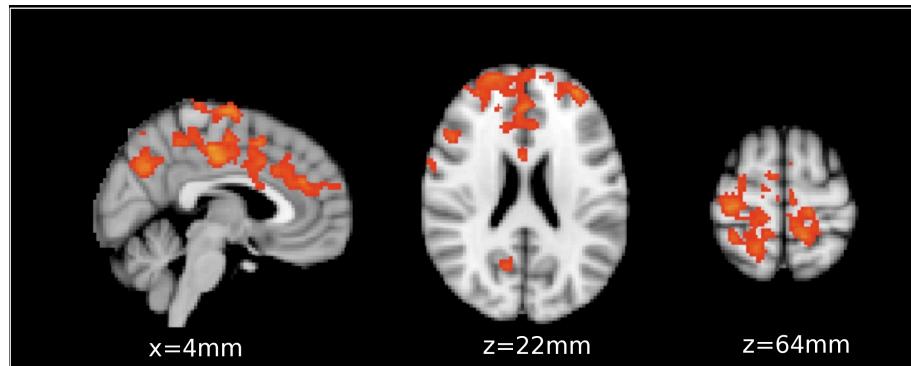
Positive correlation between the heat-evoked brain activation and the second factor reflecting the depression and catastrophising scores. Mixed-effects analysis, $Z > 2.3$, $p < 0.05$. Significant cluster was located in the middle section of the cingulate cortex.

Fig. 3.18: Correlation between heat-evoked brain activation and the fourth factor



Negative correlation between the heat-evoked brain activation and the fourth factor representing subjective perception of clinical status. Mixed-effects analysis, $Z > 2.3, p < 0.05$. Significant clusters were located in the ipsilateral putamen, the posterior insular cortex, and bilaterally in the thalamus (cross-section at $z=10$ mm).

Fig. 3.19: Difference in brain activation in response to pressure pain between depressed and non-depressed patients



Pressure-evoked pain, group difference between currently depressed and never depressed patients. Two-sample unpaired t-test, depressed > non-depressed contrast. Fixed-effects analysis, $Z > 2.3, p < 0.05$. There was a more extensive activation in the depressed patients bilaterally in the primary motor and primary somatosensory cortices, the supplementary motor area, the frontal poles, the anterior and mid-cingulate cortices, and the precuneus.

3.5.1 Clinical measures

The daily pain intensity reported by patients correlated positively with the disease activity measured with the DAS28, which is consistent with a clinical study by Leeb and colleagues (Leeb et al., 2007). It also correlated with the duration of joint stiffness, as the stiffness is associated with pain in RA (Khan et al., 2009).

However, there was no correlation between the reported daily pain and levels of the inflammatory markers. A lack of association between the reported pain and objective measures of inflammation such as inflammatory markers or swollen joint count has been described previously by Thompson and colleagues (Thompson and Carr, 1997). Also Rojkovich and colleagues (Rojkovich and Gibson, 1998) observed no correlation between pain and inflammatory markers in RA. In their study, the inflammatory markers correlated with the pain at night rather than with the daily pain at rest and during movement.

In our study, daily pain intensity was higher in women than in men which is consistent with the literature (Ahlmén et al., 2009; Fillingim et al., 2009).

3.5.2 Depression and catastrophising scores

Depression scores

Patients had higher depression scores on the Beck Depression Inventory than controls, which is consistent with results of earlier studies (Edwards et al., 2009; Dickens et al., 2002).

Depression scores in the patient group did not correlate with the daily pain intensity; however, a trend was present for female subjects after stratifying by gender. An influence of gender on chronic pain perception has previously been reported (Riley et al., 2001; Hirsh et al., 2006). A correlation between the severity of depressive symptoms and clinical pain has been described in chronic lower back pain patients (Clauw et al., 1999), and RA (Miwa et al., 2002). The reason why the correlation was present in the female group is probably related to stronger association between pain and depression in women (Fill-

ingim et al., 2009), and partly to a larger female sample. The fact that we did not observe strong correlations in the whole patient group may be due to the fact that the patients in our study had severe RA with high intensity of daily pain, and high degree of depressive symptoms, whereas in the study by Miwa and colleagues (Miwa et al., 2002), the disease activity and pain intensity were lower. Our patients had also more severe depressive symptoms than patients in the study by Clauw and colleagues (BDI mean 8.5 (SD 6.5) versus median 12 (IQR 6.5), respectively). It is likely that a high degree of inflammation changes the relationship between daily pain and depressive symptoms, as proinflammatory cytokines affect both pain and mood (Watkins and Maier, 2003; Dantzer and Kelley, 2007). Moreover, clinical depression, past and present, may affect the associations between clinical pain and depressive symptoms (Zautra et al., 2007). Finally, the currently depressed patients were treated with antidepressants, which are known to have analgesic properties (McQuay et al., 1993).

Depression scores did not correlate with disease activity or inflammatory markers even after stratifying by gender. Also Penninx and colleagues (Penninx et al., 2003) observed that the serum level of IL-6, but not CRP, correlates with severity of depressive symptoms. However, interactions between disease activity, assessed using joint count, and depression have been reported previously by Parker and colleagues (Parker et al., 1992a). The discrepancies may be due to the fact that Parker and colleagues used joint counts as a measure of disease activity, whereas we and Penninx and colleagues have used inflammatory markers.

Effect of clinical depression on pain processing in RA

In our study, depressed patients were not excluded as there is a strong association between depressive symptoms and chronic pain, and depression is a common co-morbidity in chronic pain conditions (Dickens et al., 2002; Katz and Yelin, 1993). Six out of 36 patients were clinically depressed at the time of the study, which is similar to the ratio reported in other studies (Soederlin et al., 2000; Hyrich et al., 2006a).

Depressed patients had a higher tender joint count, and a higher proportion of tender joints in relation to swollen joints. Association between the tender joint count and depressive scores has been previously reported by Schweinhardt and colleagues (Schweinhardt et al., 2008a) using a preliminary subset of these patients. As tender joint count reflects mainly disease activity and the amount of pain in RA, this would suggest that the depressive symptoms are associated with the general pain in RA. Higher levels of reported clinical pain in depressed patients have been observed in patients with chronic musculoskeletal pain (Wilson et al., 2002), and in RA patients (Conner et al., 2006).

The daily pain, duration of joint stiffness, disease activity, ESR, and catastrophising scores did not distinguish patients with and without the current diagnosis of depression. This is consistent with the results of a study by Tennen and colleagues (Tennen et al., 2006) who have reported that fibromyalgia patients with a diagnosis of depression do not differ in pain levels from those without, but their association between mood and pain is stronger, i.e., they have lower mood on days with more pain. However, our study is at odds with the study by Hider and colleagues (Hider et al., 2009) who observed that depressed RA patients have higher disease activity scores. A lack of correlation between depression and disease activity may be due to the fact that patients in our study had high disease activity as well as high depression scores; therefore, some of the correlations may not be observed. Further data are needed to resolve this.

Catastrophising scores

In our study, patients scored higher on the Pain Catastrophising Scale than controls. In the patient group, catastrophising did not correlate with disease activity or ESR, although positive correlations between catastrophising and disease activity have been reported in other studies (Parker et al., 1991, 1992a). This is probably due to the fact that all the patients in our study had high disease activity and high levels of inflammation. Therefore, if catastrophising is a tendency that becomes active during stress or in response to salient stimuli, it was probably fully present in the patients in our study.

We did not observe a correlation between the catastrophising score and daily pain intensity, unless the analysis was performed in the female and male patients separately. There was a trend for correlation between daily pain and catastrophising in the male RA patients. Other studies have demonstrated that patients who score high on catastrophising tend to report more pain (Lefebvre and Keefe, 2002; Covic et al., 2000; Keefe et al., 1991, 1989). We have also observed a negative correlation in male RA patients and a trend in female patients between catastrophising scores and temperature chosen to evoke moderate pain. This is in line with a study by Edwards and colleagues (Edwards et al., 2006) who reported that catastrophising is related to a lower pain threshold and reduced pain tolerance in chronic pain patients. This confirms that both gender and catastrophising contribute to clinical pain sensitivity as has been demonstrated by George and colleagues (George and Hirsh, 2009). They described this effect for clinical pain rather than experimental pain. It is difficult to compare their study with ours because of different stimuli used. Another reason why we did not observe this effect for the pressure strength is probably due to a lack of statistical power as the pressure strength was assessed with a simple ordinal scale with a narrow range. Finally, in our study, a small sample size did not allow a multi-variate analysis to be used effectively, and a non-parametric test lacked sensitivity, therefore, we did not observe these relationships in the whole dataset.

3.5.3 Psychophysical data

3.5.3.1 Stimulation

In the patient group, strength of pressure stimuli and temperatures did not correlate with disease activity or inflammatory markers. There was a negative correlation between catastrophising scores and temperature in male patients and a near significant negative correlation in female patients. The correlation with depression scores was not significant, even after stratifying for gender. None of the measured clinical or psychological variables significantly correlated with the pressure strength but this may be due to a crude scale used to calibrate pressure.

The strength of pressure stimuli was lower in patients who could not refrain from taking pain-killers on the day of the baseline visit. So despite the fact that these patients took pain-killers on the day of the scan they still have chosen lower pressure strength to evoke pain they perceived as moderately painful. There was no effect of pain-killers on temperature perceived as moderately painful. However, the factor analysis showed that the strength of stimuli, both pressure and heat, was negatively associated with the factor representing the subjective perception of clinical status, i.e., intensity of daily pain and patient's perception of general health (this is probably a dimension on which patients decide whether to take a pain-killer). This suggests that patients who reported high subjective disease activity and high intensity of daily pain have rated lower temperature and lower pressure as moderately painful. A negative correlation between daily pain and stimulus strength was significant for temperature but not for pressure, but this may be because of the crude scale used to quantify the pressure strength, as has been discussed earlier.

The temperatures required to evoke moderate pain was significantly lower in the patient group. This would suggest that there was thermal hyperalgesia to suprathreshold stimuli in RA patients, when stimuli were applied to a neutral site. The temperatures were inversely correlated with the daily pain, which suggests that the patients who had more clinical pain have perceived lower temperatures as moderately painful or were able to tolerate lower temperatures. This is not in line with a study on lower back pain by George and colleagues (George et al., 2007) in which clinical pain intensity did not correlate with thermal pain threshold and tolerance. However, in our study temperatures were associated not only with daily pain intensity, but also with depression and catastrophising scores. It is likely that the affective and cognitive state affected the report of clinical pain and temperatures chosen as moderately painful.

In our study, temperatures perceived as moderately painful were lower in female patients. This effect was not observed in the control group. The literature on gender effects on pain processing is not consistent (Fillingim et al., 2009). It has been reported that women have lower pain thresholds and tolerance and give higher pain ratings of exper-

imental pain (Riley et al., 1998). Lower heat pain tolerance in women was also observed in a clinical study on patients suffering from chronic back pain (George et al., 2007).

3.5.3.2 Pain ratings

Pressure stimuli were rated as moderately painful by patients, but were not painful when applied to normal, non-inflamed joints in the control group. For the stimulation-matched heat condition, the pain ratings were significantly lower in the control group. Together with a lower temperature chosen to evoke moderate pain, it confirms the presence of thermal hyperalgesia in RA. This is in line with the study by Edwards and colleagues (Edwards et al., 2009), who reported hyperalgesia to mechanical and thermal stimuli at disease-related and neutral sites in RA patients in comparison to healthy controls. Pain ratings for the perception-matched heat stimulation were not significantly different between the groups when the matched groups of patients and controls were analysed, i.e., when controlled for an effect of age and gender.

3.5.4 Imaging results

3.5.4.1 Pressure-evoked brain activation in patients versus controls

In the patient group, pressure-evoked pain resulted in a robust and extensive brain activation in the regions typically involved in pain processing (Peyron et al., 2000; Apkarian et al., 2005). The brain activation pattern in response to pressure pain in our study was similar to activation evoked by joint palpation in psoriatic arthritis in a study by Baliki and colleagues (Baliki et al., 2005).

Activation to pressure stimuli in the control group involved mainly regions responsible for sensory-discriminative processing of stimuli, such as the primary somatosensory and insular cortices (Henderson et al., 2007). The activation was more extensive than that found in response to low-intensity pain in a study by Giesecke and colleagues (Giesecke et al., 2004), however this may be related to higher field strength of our scanner.

In our study, the brain activation in response to pressure was more extensive in the patient group, as pressure was painful for patients but not painful in controls, and which is consistent with hyperalgesia and pain augmentation reported by Gracely and colleagues (Gracely et al., 2002) in fibromyalgia patients in response to stimulation-matched pressure. The differences were observed in the region involved in processing the sensory-discriminatory dimension of pain, such as the primary somatosensory and the posterior insular cortices, and the thalamus (Porro, 2003; Coghill et al., 1999), the affective dimension of pain processing, such as the anterior insular and the anterior cingulate cortices (Price, 2000; Vogt et al., 1996), and also changes in attention and orientation to stimuli, such as the precuneus and the mid cingulate cortex (Vogt, 2005). More activation in patients than in controls was also present in the brainstem, the thalamus and the striatum, the precuneus and cerebellum, as have been previously described in response to pressure pain in fibromyalgia (Gracely et al., 2002). It is possible that this activation pattern is related to secondary sensitisation, as an increased activity in the brainstem, the thalamus, the cerebellum, the primary somatosensory cortex, the anterior cingulate, and the insular cortices have been described during capsaicin induced hyperalgesia in healthy volunteers (Iadarola et al., 1998; Zambreanu et al., 2005; Baron et al., 1999). Increased activation in the insular and cingulate cortex but not in the secondary somatosensory cortex, similar to the pattern observed in our study, has been reported as an result of augmentation of nociceptive input in ongoing pain and capsaicin hyperalgesia in a study by Mohr and colleagues (Mohr et al., 2008). There was also more activation in the medial prefrontal cortex and the brainstem possibly related to altered pain modulation in RA (Gebhart, 2004).

3.5.4.2 Pressure-evoked versus heat-evoked pain in the patient group

Pressure evoked pain and heat-evoked pain were both perceived as moderately painful, and both stimuli resulted in activation of cortical and subcortical regions involved in pain processing. However, the activation in response to pressure was more extensive, which is consistent with a study by Henderson and colleagues (Henderson et al., 2006). In our

study, the differences between the pressure and heat pain were present in regions involved in stimulus identification such as the primary somatosensory cortex, as well as intensity encoding such as the thalamus and the middle insular cortex. Differences were also observed in regions involved in pain modulation such as the medial prefrontal cortex, and structures processing self-awareness and perception of one's body such as the precuneus, the superior temporal gyri, the posterior cingulate cortex, and the secondary somatosensory cortex (Behrman et al., 2004; Craig et al., 2000). Pressure-evoked pain was associated with more attention towards spatial and affective qualities of the stimulation, as it resulted with stronger activation in the precuneus and the superior parietal gyri, and the medial prefrontal cortex, respectively. Medial parietal regions have been reported to play an important role in attention and processing spatial properties of stimulation, especially in relation to self (Behrman et al., 2004). The medial prefrontal cortex is important for encoding and evaluating stimuli as well as directing attention towards emotional stimuli (Kong et al., 2006; Kalisch et al., 2006). This would suggest that there is an attention bias toward pressure pain. RA patients process the pressure pain more in the context of their physical self.

The differences might be also due to the different relation of pressure and heat pain to clinical pain. Geisser and colleagues (Geisser et al., 2007) reported that the pressure stimulation is significantly associated with clinical pain ratings, whereas the thermal pain is not. The observed differences in the activation pattern may be related also to different sensory properties of these two types of stimulation. It has been demonstrated previously that mechanical stimulation activates the primary sensory and primary motor cortices to a greater extent than during heat pain (Maihofner et al., 2006; Henderson et al., 2006).

3.5.4.3 Heat-evoked brain activation in patients versus controls

There was a similar activation pattern in response to heat in patients and controls. Both groups showed an extensive activation in the regions typically involved in pain processing, and the activation pattern was similar to the one observed by Becerra and colleagues (Becerra et al., 1999) in healthy controls in response to heat pain.

The statistical comparison of the heat-evoked brain activation in all patients and perception-matched heat-evoked activation in all controls showed more activation in controls than in patients in the contralateral posterior insular and the secondary somatosensory cortex as well as the precuneus. This is in line with the study by Jones and Derbyshire (Jones and Derbyshire, 1997) who reported a reduced activation in response to noxious heat in RA patients. The posterior insular cortex is involved in withdrawal and predicting response as well as in coding stimulus strength (Henderson et al., 2007). It also reflects the actual nociceptive input (Brooks and Tracey, 2005; Ostrowsky et al., 2002). The precuneus is a major association area involved in self-referential processing and experience of agency (Cavanna and Trimble, 2006).

For the matched subset of patients and matching controls, i.e., 23 pairs, the stimulation-matched activation was more extensive in the control group bilaterally in the thalamus, the head of caudate nucleus, in the contralateral posterior insular cortex, and the primary somatosensory cortex. All these structures encode stimulus intensity (Henderson et al., 2006, 2007; Bingel et al., 2004). The posterior insular cortex is connected with the thalamus and the sensorimotor areas (Mesulam and Mufson, 1982; Craig, 2003b). Observed differences are unlikely to reflect a lower nociceptive input in the patient group, as the groups were matched with respect of stimulus strength, and the nociceptive input was similar. Also, the peripheral nerve function is usually not altered in RA (Bekkelund et al., 1996). The comparison of the perception-matched heat condition in the matched subjects showed a more extensive activation in the control group in the thalamus and the contralateral posterior insular cortex, as in the stimulation-matched condition, but also in regions involved in attention towards stimuli such as superior parietal gyri, and the midcingulate cortex.

Less extensive activation in the patient group is in line with the findings by Jones and Derbyshire (Jones and Derbyshire, 1997) who demonstrated reduced brain activation in response to heat in RA. It is probably due to changes in central pain processing, mainly altered descending pain modulation, as there is an increase in occupancy by endogenous opioid peptides in RA (Jones et al., 1994).

Differences in brain activation between patients and controls might be also related to a reduced BOLD signal change in response to pain in the presence of ongoing pain (Apkarian et al., 2005). There may be a reduced activation in response to heat in the chronic pain patient group due to processing of ongoing, clinical pain; therefore, inhibiting the increase of the haemodynamic response to evoked pain (Derbyshire et al., 2002; Apkarian et al., 2005). The reduced activation in thalamus may be also associated with hypometabolism in the thalamus described in chronic pain by several authors (Hsieh et al., 1995; Iadarola et al., 1995; Di Piero et al., 1991).

Previous studies have reported no differences in encoding thermal stimuli between lower back pain patients and controls (Derbyshire et al., 2002), but less activation in response to heat in patients with RA (Jones and Derbyshire, 1997). Jones and Derbyshire (Jones and Derbyshire, 1997) suggested that the reduced pain response is related to the effect of chronic inflammation on central pain processing. These authors reported differences in the medial prefrontal and the anterior cingulate cortices, i.e., regions involved in descending modulation of pain, which supports the hypothesis of altered descending pain inhibition in RA. The reason why Jones and Derbyshire observed differences in different regions than those demonstrated in our study may be due to the fact that they have used innocuous thermal stimulation as a baseline whereas we used rest. This may explain why they did not show activation in regions involved in sensory-discriminative processing.

3.5.4.4 Factor analysis

A factor analysis was performed in the patient group in order to better characterise the relationships between the measured variables. Moreover, it allowed us to use all measured clinical, psychological and psychophysical variables in the GLM; therefore, to better interpret the pain-evoked brain response. Moreover, factor analysis reduces the measured variables into a few underlying factors, which are orthogonal to each other. A factor analysis was chosen because standard models, i.e., demeaned values of measured variables entered into the GLM as covariates of interest were not suitable. These models were over-

simplistic when only one variable was used, or too difficult to interpret when several variables were entered. Moreover, the size of the sample in our study did not allow for entering all the measured variables into the model, and required arbitrary choosing only some of them. In addition, some of the variables, such as disease activity score and ESR correlated with each other, making the GLM inefficient. Therefore, factor analysis offered an alternative approach to modelling the effect of clinical and psychological measures on pain-evoked brain activation.

The pressure-evoked activation correlated only with the factor reflecting the objective disease activity. Positive interactions were observed in the ipsilateral anterior insular cortex. This region, especially in the right hemisphere, is suggested to be involved in interoception, i.e., processing sensory information regarding the physiological state of the body, as well as subjective awareness of internal feelings or state (Craig, 2003a, 2002; Critchley et al., 2004). Anterior insula has connections to autonomic and limbic regions such as the amygdala and entorhinal cortex, ventral striatum, and autonomic regions in the brainstem (Mesulam and Mufson, 1982; Chikama et al., 1997; Jasmin et al., 2004). It has been suggested that these regions play an important role in chronic pain processing (Schweinhardt et al., 2006a).

The heat pain-evoked activation correlated positively with three factors. The inflammatory dimension, i.e., the first factor, correlated with activation mainly in the midcingulate, and to a lesser degree with the primary sensory and primary motor cortices. The midcingulate and the primary motor cortex activation may reflect a withdrawal and inhibition of motor response during pain (Svensson et al., 2003b; Beckmann et al., 2009). The midcingulate is the section of the cingulate cortex that is most often activated in pain studies, and is involved in the cognitive aspect of pain and withdrawal (Beckmann et al., 2009). Activation in this region is not unique to noxious stimuli. The midcingulate plays an important role in evaluation of sensory stimuli and orienting the body in response to sensory stimuli (Vogt, 2005). A similar cluster in the midcingulate correlated with the third factor, representing the depression and catastrophising scores. These finding suggest that inflammation, depression and catastrophising affect experimental pain processing by changing evaluation of pain. It has been suggested that catastrophising mediates

the effect of depression on the evaluative dimension of pain, as well as on the affective dimension of pain (Geisser et al., 1994; Gracely et al., 2004). It is possible that the thermal stimuli used in our study were not very unpleasant, therefore, we did not observe an effect on the affective pain processing. However, unpleasantness was not assessed in this study.

The fourth factor, correlated negatively with activation bilaterally in the thalamus, and ipsilaterally in the putamen and the posterior insular cortex. The thalamus and the putamen are the relay centres for noxious input, and integrate sensory input and motor response. The putamen receives nociceptive and non-nociceptive sensory information, and encodes stimulus intensity (Bingel et al., 2004). The posterior insular cortex is connected to the thalamus (Craig, 2003b) and sensorimotor cortex (Mesulam and Mufson, 1982), and is associated with the sensory aspects of nociceptive input (Brooks and Tracey, 2005; Ostrowsky et al., 2002). Activation in the posterior insular cortex reflects the actual nociceptive input (Brooks and Tracey, 2005; Ostrowsky et al., 2002), and it is also involved in a withdrawal response (Henderson et al., 2007). The fourth factor reflected the subjective perception of clinical status, but it was also inversely related to the stimuli strength. This explains why there was a negative correlation between this factor and brain regions encoding the nociceptive input.

The reason why the pressure condition correlated only with one factor whereas the heat condition correlated with three may be due to larger heterogeneity and more variance in the pressure condition (different joints, different degrees of inflammation, swelling, joint damage, different degree of effusion).

3.5.4.5 Depression and augmentation of pain

The effect of depression was present only during the pressure pain condition, which would suggest that the depressive symptoms affect processing of pressure pain but not heat pain, as described by Schweinhardt and colleagues (Schweinhardt et al., 2008a). This may be related to the fact that the pressure pain was more related to the clinical pain, and

perhaps was more salient, more potentially damaging, than the artificial, purely experimental heat pain.

In our study, depressed patients in comparison to non-depressed patients showed more brain activation bilaterally in the primary motor and somatosensory cortices, the anterior and midcingulate cortex, the superior parietal gyri, and the precuneus.

What is interesting, depressed patients showed more activation in the cortical midline structures, i.e., the cingulate cortex and the precuneus, which are involved in affective, cognitive and self-referential processing (Northoff and Bermpohl, 2004; Beckmann et al., 2009; Vogt, 2005). It has been demonstrated that the negative mood increases affective processing of painful stimuli and contributes to the enhanced perception of pain (Rainville et al., 2005). However, our results suggest that depression changes not only affective processing of pain, but also the cognitive dimension and attention.

3.6 Main findings

- Daily pain intensity correlated positively with the disease activity score but not with inflammatory markers, and was higher in female patients. Daily pain correlated negatively with a temperature perceived as moderately painful. Relationships between catastrophising and depression and daily pain became significant only after stratifying for gender.
- Currently depressed patients in comparison to patients who were never depressed had a higher tender joint count and a higher tender to swollen joint ratio.
- In the patient group, pressure and heat stimulation evoked an extensive activation in the regions typically involved in pain processing.
- The pressure condition resulted in a significantly more extensive activation in patients than in controls and the observed differences in activation suggested not only stronger input but also changes in central processing of pain in RA.
- For the heat condition, there was more activation in the controls than in patients, most likely due to an altered descending pain modulation in RA.

- Factor analysis: The pressure pain evoked activation in the posterior insular cortex correlated with the objective clinical status, suggesting an important role of this region in chronic pain. For the heat evoked activation, we demonstrated that inflammation, as well as depression and catastrophising correlated with brain regions involved in attention and the cognitive processing of sensory stimuli.
- Clinical depression had an effect only on the pressure pain condition and was associated with more extensive activation in the regions involved in self-referential processing and attending to salient stimuli.

Chapter 4

SHORT-TERM EFFECTS OF ANTI-TNF TREATMENT

4.1 Introduction

Anti-TNF therapy results in a rapid improvement in clinical measures in RA including pain, disease activity, and inflammation. The changes can be observed as early as within the first four weeks after the beginning of the treatment (Feldmann et al., 1996). However, the response is variable and approximately 20-50% of patients do not respond to this therapy (Feldmann, 2002; Felson et al., 1995). As the anti-TNF treatment is expensive and has some potentially serious side effects, the current guidelines recommend that it should be stopped if there is no effect within three months (Ledingham et al., 2005). Currently, there are no clinical markers that could identify the patients for whom the anti-TNF therapy will be effective.

4.2 Aims and hypotheses

The aim of this chapter was to analyse changes in processing of evoked pain in RA at one month after the beginning of anti-TNF treatment. We also wanted to investigate whether any of the characteristics of pain-evoked brain activation at the baseline are associated with the clinical effectiveness of the therapy.

4.3 Methods

4.3.1 Participants

For the analyses in this chapter we used data of the RA patients ($n = 23$) who completed the baseline visit PAT_{BL} and the short-term visit PAT_{ST} . The short-term visit was scheduled between two and four weeks after the start of treatment¹.

In this group of patients there were 18 women and five men; the median age was 63.0 years (IQR 22.0), and the median disease duration was 17.0 years (IQR 11.0).

Seven patients did not refrain from taking painkillers before the baseline scan, and five before the second scan. Two patients were clinically depressed, and were treated with antidepressants.

4.3.2 Experimental protocol

The pre-scanning assessment and scanning protocol were described in detail in the Methods chapter in sections 2.2.5 and 2.2.6.

4.3.3 Analysis of clinical, psychological, and psychophysical data

4.3.3.1 Differences between visits

Short-term changes in clinical, psychological, and psychophysical measures were investigated using the Wilcoxon Signed Ranks Test.

A change between a value at the baseline PAT_{BL} and at the short-term PAT_{ST} visit was also calculated for each variable, and the difference PAT_{BL-ST} was subsequently used in correlation and in factor analysis.

¹ 13 out of 36 patients completed only the baseline visit: 9 did not return for the subsequent scans (4 dropped out, 5 were missed due to a gap in the study), 3 did not ever begin the treatment, 1 had an adverse reaction to the treatment.

4.3.3.2 Correlation analysis

To investigate the interactions between the changes in pain scores, clinical, psychological, and psychophysical variables exploratory correlations were calculated between the differences in measured variables between the baseline and the short-term visit PAT_{BL-ST} using the Spearman's Rank Correlation Coefficient, ρ .

4.3.3.3 Factor analysis

As several changes in the measured variables were correlated, a factor analysis was performed to investigate the underlying dimension in the observed changes. Another advantage of using a factor analysis was that it reduced the data to fewer dimensions, which were used as additional regressors in the analysis of imaging data.

Changes in the following variables were used in the factor analysis: disease activity score (DAS28), tender and swollen joint counts, daily pain intensity, duration of joint stiffness, inflammatory markers (ESR and CRP), general health rating (from the DAS28), pain intensity ratings for heat and pressure, depression and catastrophising scores.

4.3.3.4 Improvement

An improvement was defined as a reduction of the disease activity score by more than 1.2. The differences between the group of patients who did and who did not improve were tested using the Mann-Whitney U test.

4.3.3.5 Response at three months

Patients were assessed by their consultants three months after the beginning of the treatment. Those patients who were classified by their consultants as responders and continued their original treatment were referred to in this study as responders, and those who did not respond and had their medication changed were called non-responders. The Mann-Whitney U test was used to compare the group that did and did not respond.

4.3.4 Analysis of imaging data

4.3.4.1 Differences between visits

To assess short-term effects of the treatment, a two-sample paired t-test was performed between the first-level results from the baseline PAT_{BL} and from the short-term PAT_{ST} visit. The analysis was performed for pressure- and heat-evoked pain, separately.

4.3.4.2 The effect of changes in clinical and psychological scores on pain-evoked activation

To investigate the influence of changes in clinical and psychological scores on change in pain-evoked brain activation, a three-level analysis was performed using factor scores from the factor analysis as additional explanatory variables.

First, a change between the first-level results at the baseline PAT_{BL} and at the short-term PAT_{ST} visit was calculated for each patient using a second-level fixed-effects analysis. The resulting difference PAT_{BL-ST} for each patient was used as an input into a third-level analysis. In the third-level analysis, one common regressor was used to model the group mean and additional regressors represented the demeaned factor scores from the factor analysis of the clinical and psychological data. Contrasts were set to model a positive and negative correlation between the brain activation change PAT_{BL-ST} and each factor. The analysis was done for pressure- and heat-evoked pain, separately.

4.3.4.3 Improvement

A two-sample unpaired t-test was used to test for differences in the first-level results between patients who improved, and those who did not. The analysis was done for the results from the baseline PAT_{BL} and for differences between the visits PAT_{BL-ST} ², separately.

² The contrast was set in both directions but we refer to it as PAT_{BL-ST} because we expected to observe a decrease in activation after the treatment.

4.3.4.4 Response at three months

A two-sample unpaired t-test was used to test for differences in the first-level results between patients who responded at three months, and those who did not. The analysis was done for the results from the baseline PAT_{BL} and for differences between the visits PAT_{BL-ST} .

4.4 Results

4.4.1 Clinical, psychological, and psychophysical data

Within the first four weeks after the start of therapy, there was a significant reduction of pain ratings for pressure- and for heat-evoked pain, daily pain intensity, disease activity (DAS28), including tender and swollen joint counts, and inflammatory markers. There was also a decrease in depression and catastrophising scores (Table 4.1).

The median time between the beginning of the treatment and the second visit was 18 days (IQR 6).

Table 4.1: Change in clinical, psychological, and psychophysical variables between visits in the patient group

Variable		BL	ST	Z-value	P-value
Disease activity	mean (SD)	6.35 (0.83)	5.06 (0.97)	-4.167	< 0.0005
Tender joint count	median (IQR)	11.0 (6)	10.0 (6)	-3.734	< 0.0005
Swollen joint count	median (IQR)	11.0 (8)	8.0 (6)	-3.193	0.001
Erythrocyte sedimentation rate, $\frac{mm}{h}$	median (IQR)	34 (33)	23 (27)	-3.303	0.001
C-reactive protein, $\frac{mg}{l}$	median (IQR)	15.0 (24.5)	8.5 (20.5)	-2.62	0.009
Joint stiffness, minutes	median (IQR)	60 (75)	15 (60)	-3.52	< 0.0005
Daily pain intensity	median (IQR)	6.5 (2.5)	4.5 (3.0)	-3.435	0.001
Pressure pain rating	median (IQR)	5.0 (1.6)	4.0 (2.2)	-2.804	0.005
Heat pain rating	median (IQR)	6.0 (1.5)	5.5 (2.0)	-2.7	0.007
Depression score	median (IQR)	10.0 (7)	6.0 (8)	-2.268	0.023
Catastrophising score	median (IQR)	14.0 (23)	5.0 (9)	-2.286	0.022

Median and mean values at the baseline PAT_{BL} , and short-term PAT_{ST} after treatment, and Z- and

p-values of the Wilcoxon Signed Rank test between the values for the two visits.

4.4.1.1 Differences between drugs

As only two patients were treated with Infliximab, a group comparison was performed between patients treated with Adalimumab ($n = 10$) and Etanercept ($n = 11$). No difference was found either for the baseline values or for the change in values for the following variables: pain ratings, daily pain intensity, depression and catastrophising scores, diseases activity scores or inflammatory markers.

4.4.1.2 Correlations

Changes in disease activity score, inflammatory markers, and Patient Global Impression of Change were correlated. There was also a correlation between the depression scores, intensity of daily pain, the erythrocyte sedimentation rate (Table 4.2).

Change in pressure- and heat-evoked pain ratings were not correlated with one another, and they did not correlate with a change in any of the clinical or psychological measures.

Table 4.2: Correlations between changes in clinical, psychological, and psychophysical data

Variable	Correlation, ρ										
	1	2	3	4	5	6	7	8	9	10	11
1. Δ disease activity	-										
2. Δ tender joint count	0.60	-									
3. Δ swollen joint count	0.41	0.26	-								
4. Δ erythrocyte sedimentation rate	0.64	0.09	0.23	-							
5. Δ daily pain	0.48	0.26	-0.11	0.44	-						
6. Δ joint stiffness	0.23	0.28	-0.25	0.08	0.50	-					
7. Δ pressure pain rating	0.02	0.09	-0.09	-0.28	0.13	0.13	-				
8. Δ heat pain rating	0.05	-0.15	-0.08	0.04	0.36	-0.11	0.17	-			
9. Δ catastrophising score	0.39	0.46	0.27	0.24	0.35	0.19	0.20	0.45	-		
10. Δ depression score	0.6	0.18	0.24	0.72	0.68	0.19	0.20	0.45	0.30	-	
11. PGIC	0.68	0.64	0.19	0.25	0.64	0.17	0.21	0.15	0.54	0.44	-

Spearman's ρ correlations between changes in clinical, psychological and psychophysical variables in the patient group. Significance at the $p < 0.05$ level (corrected for multiple comparisons using Bonferroni correction $0.05/12 = 0.004$) marked in bold font.

4.4.1.3 Factor analysis

Changes in the variables loaded on four main factors (Figure 4.1) and this model explained 72.8% of variance in the measured variables. The Kaiser-Meyer-Olkin Measure of Sampling Adequacy was 0.52; therefore it was appropriate to carry out a factor analysis. The closer the Kaiser-Meyer-Olkin Measure is to 1 the more likely it is that the pattern of correlations is compact and that the factor analysis will give reliable factors. Values above 0.5 are acceptable.

The Bartlett's Test of Sphericity was significant at $p < 0.001$; therefore the null hypothesis that the variables in the correlation matrix are uncorrelated could be rejected. The Bartlett's Test of Sphericity tests whether there are any relationships between the variables, i.e., that some of variables are correlated.

The first factor had an eigenvalue of 4.02 and explained 33.5% of the variance in the measured variables. It corresponded to changes in pain and psychological variables. The main variables loading on this factor were: change in daily pain intensity, change in the subjective perception of general health, duration of joint stiffness, as well as a change in depression and catastrophising scores. Tender joint count loaded partly on this factor but it was more related to the third factor together with a change in disease activity score.

The second factor, an eigenvalue of 1.78 and explained 14.9% of the variance, represented a change in inflammatory markers. Changes in depressive score loaded partly on this factor, but depression was mainly represented by the first factor.

The third factor represented changes in the objective clinical status, including change in disease activity score, and tender and swollen joint counts. The eigenvalue of the third factor was 1.7 and it explained 14.2% of the variance.

Changes in pain ratings of pressure and heat pain loaded on the fourth factor. The last factor had an eigenvalue of 1.2 and it explained 10.3% of the variance.

4.4.1.4 Improvement

Twelve patients improved within the first four weeks of treatment, and their disease activity score decreased by at least 1.2.

Fig. 4.1: Factor analysis for changes after treatment

	Component			
	1	2	3	4
joint stiffness	.816	-.030	-.211	-.019
catastrophising	.766	.081	.171	-.150
daily pain intensity	.703	.379	-.008	.310
general health	.687	.116	.222	.304
depression score	.594	.515	.205	.258
C-reactive protein	.032	.877	-.112	-.025
ESR	.193	.871	.325	-.112
swollen joint count	-.245	.078	.809	-.093
disease activity score	.372	.242	.762	.161
tender joint count	.542	-.275	.646	-.083
rating for heat pain	.055	.165	-.111	.788
rating for pressure pain	.055	-.269	.084	.721

Changes in the clinical and psychological variables. Rotated component matrix. Extraction method: Principal Component Analysis; rotation method: Varimax with Kaiser normalisation.

There were no differences between the patients who did and did not improve in baseline values of the following variables: inflammatory markers, psychological scores, daily pain, disease activity, and tender or swollen joint count. There were two patients who were clinically depressed at the time and completed the short-term visit; these patients did not improve.

Patients who improved showed a larger reduction (between baseline and the short-term visit) in daily pain intensity, disease activity score, ESR, depression score, tender joint count but not in catastrophising score or swollen joint count (Table 4.3).

4.4.1.5 Response at three months

After three months of therapy patients were assessed by their treating consultants. Five patients were classified as non-responders; four of these patients had their medication changed from Adalimumab to Etanercept, and one from Etanercept to Adalimumab.

Responders did not differ from non-responders in baseline values or a change in any clinical or psychological measures, except for higher tender joint count in non-responders

Table 4.3: Differences in clinical and psychological measures between patients who did and did not improve.

<i>Variable</i>	<i>Improvement</i>	<i>No improvement</i>	<i>P-value</i>
Δ disease activity	1.9 (0.9)	0.4 (0.5)	< 0.0005
Δ erythrocyte sedimentation rate	22.5 (23.5)	4 (18)	0.001
Δ tender joint count	5.5 (4.8)	3 (5)	0.027
Δ swollen joint count	5.0 (5.75)	3 (6)	0.347
Δ daily pain	2.3 (2.8)	1 (2)	0.009
Δ depression score	4 (4)	0 (3)	0.002
Δ catastrophising score	3 (10)	2 (5)	0.193
PGIC	2 (2)	1 (1)	0.009

Median values and interquartile range for a change between the baseline and short-term PAT_{BL-ST} visit in the patient group who did and did not improve, and p-value of the Mann–Whitney U test (2-tailed) for a between-visits change.

at the baseline (the Mann–Whitney U test, $p = 0.012$), and at the and short-term ($p = 0.037$) visit, but there was no significant change between the visits ($p = 0.857$).

4.4.2 Imaging results

4.4.2.1 Change in activation after treatment

For the pressure-evoked brain activation, there was no difference between the first-level results from the baseline visit and the short-term visit, a two-sample paired t-test, either for the $PAT_{BL} > PAT_{ST}$ or for the $PAT_{ST} > PAT_{BL}$ contrast.

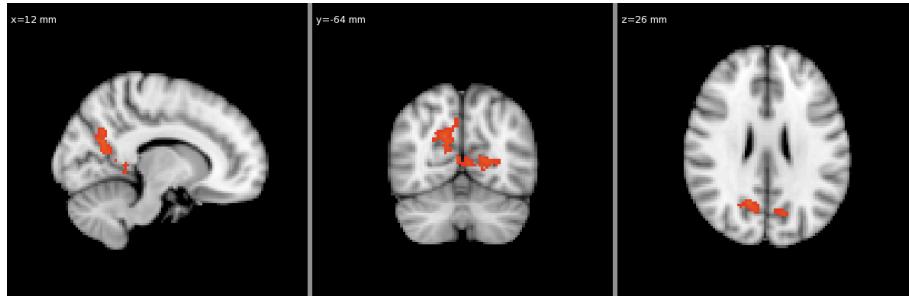
For the heat-evoked pain, there was a change of activation in the precuneus and the posterior cingulate cortex for the $PAT_{ST} > PAT_{BL}$ contrast (Figure 4.2), which reflects a reduction of deactivation in this region (Figure 4.3). There was no difference for the opposite contrast.

4.4.2.2 Factor analysis

Pressure-evoked brain activation

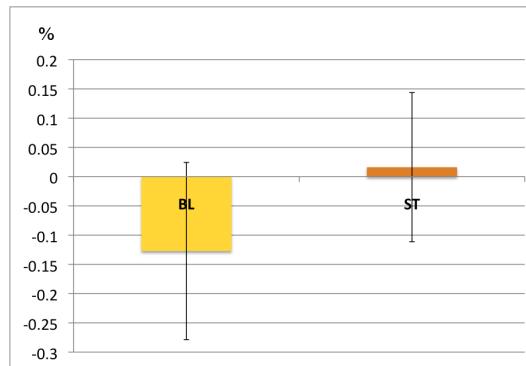
Changes in the pressure-evoked brain activation, i.e., baseline > short-term visit, correlated only with the first factor representing change in pain and psychological scores. This

Fig. 4.2: Change in heat-evoked brain activation after treatment



Change of activation in response to heat. A two-sample paired t-test, short-term visit versus baseline; $PAT_{ST} > PAT_{BL}$ contrast. Mixed-effects analysis, $Z > 2.3, p < 0.05$. Significant clusters were located bilaterally in the precuneus and the posterior cingulate cortex.

Fig. 4.3: Change in heat-evoked brain activation after treatment in the precuneus



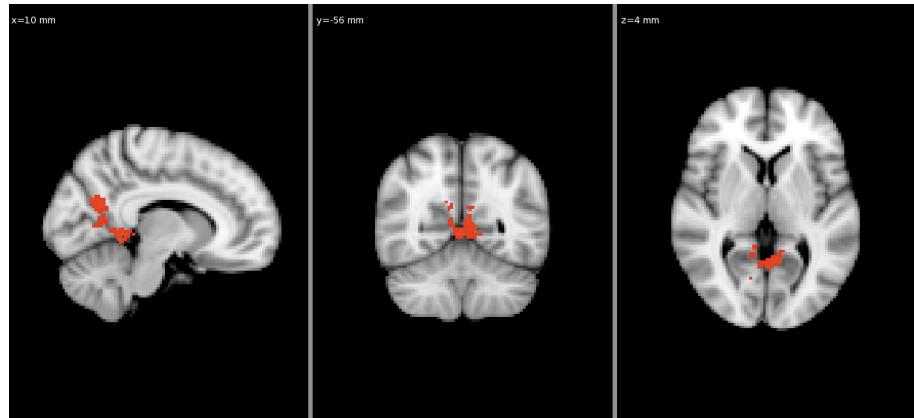
Percentage signal change in the precuneus during the heat condition. The mean and standard deviation for the values at the baseline PAT_{BL} and short-term PAT_{ST} visit. Signal change estimated within the significant cluster from the paired analysis.

factor correlated negatively with signal changes in the posterior cingulate cortex and the precuneus (Figure 4.4). There was no correlation between changes in pressure-evoked brain activation and any other factor.

Heat-evoked brain activation

For the heat-evoked pain there was a positive correlation between the second factor representing a change in inflammation, and a signal change bilaterally in the posterior section

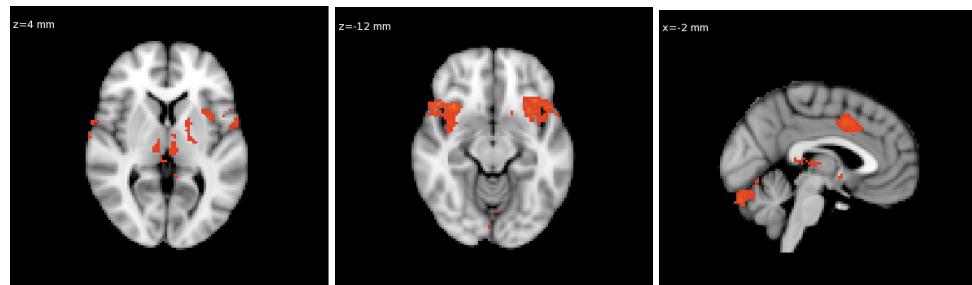
Fig. 4.4: Changes in pressure-evoked activation correlating with changes in pain and psychological factors



Changes in brain activation in response to pressure that correlated negatively with the first factor representing change in pain and psychological scores. Mixed-effects analysis, $Z > 2.3, p < 0.05$. Significant clusters were located in the posterior cingulate cortex and the precuneus.

of the anterior cingulate cortex, the anterior insular cortex, the thalamus, and in the contralateral striatum (the pallidum and the putamen) (Figure 4.5). There was no correlation between changes in brain activation and any other factor.

Fig. 4.5: Changes in heat-evoked activation correlating with changes in inflammation



Changes in brain activation in response to heat that correlated positively with the second factor representing a change in inflammation. Mixed-effects analysis, $Z > 2.3, p < 0.05$. Significant clusters were located bilaterally in the anterior cingulate cortex, the insular cortex, the thalamus, the contralateral pallidum, and the putamen.

4.4.2.3 Improvement and response

Improvement

There was no difference in brain activation at the baseline PAT_{BL} either for pressure or for heat, between patients who improved ($n = 12$) and those who did not improve ($n = 11$) at the short-term visit. There was also no difference when a more sensitive fixed-effects analysis was used.

Response

We also performed a comparison of activation at the baseline and change in activation after treatment between patients who did not respond to the treatment at three months.

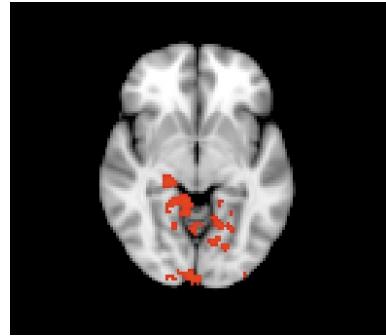
Pressure-evoked pain

For the pressure-evoked activation at the baseline, there was a more activation in responders in the ipsilateral hippocampus and bilaterally in the lingual gyri for the mixed-effects analysis (Figure 4.6). No region showed stronger activation in non-responders.

For the more sensitive fixed-effects analysis, there was more extensive activation in the responders group in the ipsilateral hippocampus, and bilaterally in the amygdala, insular cortices, and lingual gyri (Figure 4.7). For the opposite contrast, there was more activation in the non-responders group in the medial prefrontal cortex, bilaterally (Figure 4.8).

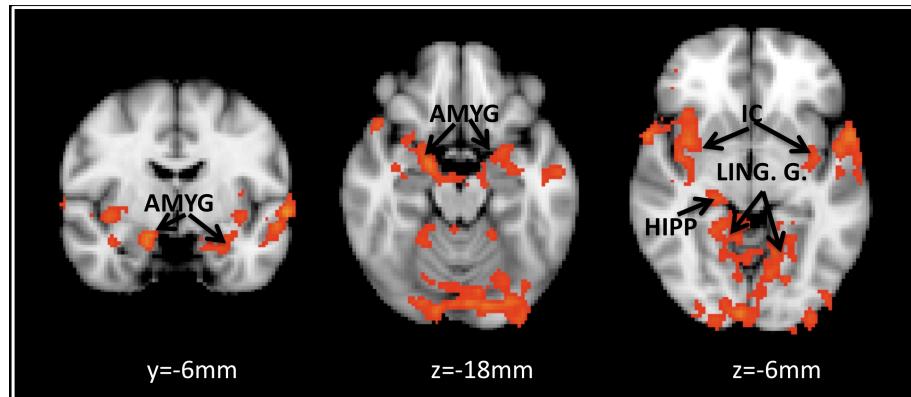
There was no difference in the change in activation between the baseline and the short term visit PAT_{BL-ST} , either for the mixed- or fixed-effects analysis. There were only sub-threshold changes observed in the ipsilateral insular cortex, the hippocampus, the thalamus and striatum in responders (Figure 4.9), and a change in the medial prefrontal cortex in non-responders (Figure 4.10).

Fig. 4.6: Differences in pressure-evoked brain activation between responders and non-responders at baseline



Differences in pressure-evoked brain activation between responders and non-responders; *responders > non-responders* contrast. Mixed-effects analysis, $Z > 2.3, p < 0.05$. Significant clusters were located in the ipsilateral hippocampus and the lingual gyri.

Fig. 4.7: Differences in pressure-evoked brain activation between responders and non-responders at baseline

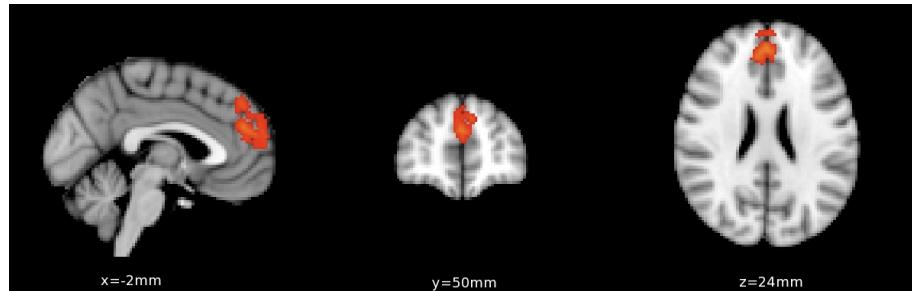


Differences in pressure-evoked brain activation between responders and non-responders; *responders > non-responders* contrast. Fixed-effects analysis, $Z > 2.3, p < 0.05$. Significant clusters were located bilaterally in the hippocampus (HIPP), the amygdala (AMYG), insular cortex (IC), and lingual gyri (LINGUAL G.).

Heat-evoked pain

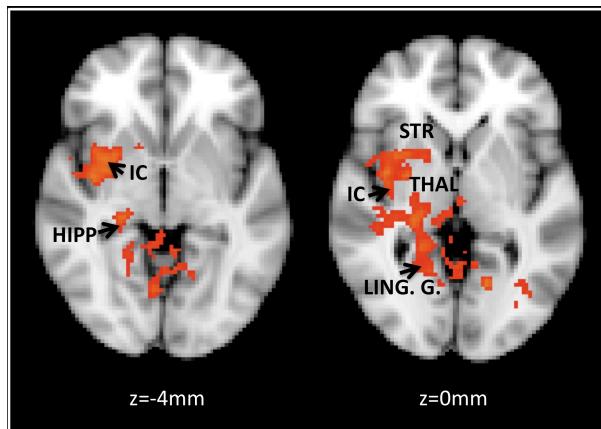
For the heat-evoked brain activation at the baseline visit, there was no difference between responders and non-responders when the mixed-effects analysis was used. For the fixed-effects analysis, there was more extensive activation in the responders group in

Fig. 4.8: Differences in pressure-evoked brain activation between non-responders and responders at baseline



Differences at baseline in pressure-evoked brain activation between responders and non-responders; *non-responders > responders* contrast. Fixed-effects analysis, $Z > 2.3, p < 0.05$. Significant clusters were located bilaterally in the medial prefrontal cortex.

Fig. 4.9: Differences in changes in pressure-evoked brain activation between responders and non-responders

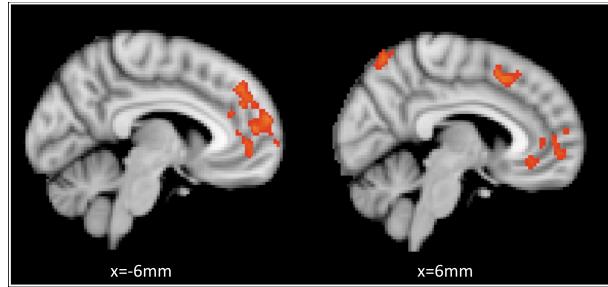


Differences in changes in the pressure-evoked brain activation after treatment between responders and non-responders; *responders > non-responders* contrast. Fixed-effects analysis, $Z > 1.8, p < 0.05$. Significant clusters were located ipsilaterally in the hippocampus (HIPP), the insular cortex (IC), the striatum (STR), the thalamus (THAL), the posterior cingulate cortex, and the lingual gyri (LING. G.).

the ipsilateral insular cortex and bilaterally in the temporal poles (Figure 4.11). There was no difference for the opposite contrast either for mixed- or fixed-effects analysis.

There was more change in activation to heat between the baseline and the short-term visit in the responders group in the contralateral thalamus, and in the anterior insular and

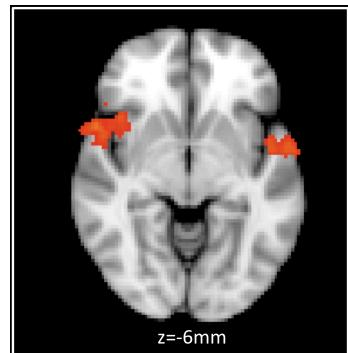
Fig. 4.10: Differences in changes in pressure-evoked brain activation between non-responders and responders



Differences in changes in the pressure-evoked brain activation after treatment between responders and non-responders; *non-responders > responders* contrast. Fixed-effects analysis, $Z > 1.8, p < 0.05$. Significant clusters were located bilaterally in the medial prefrontal cortex.

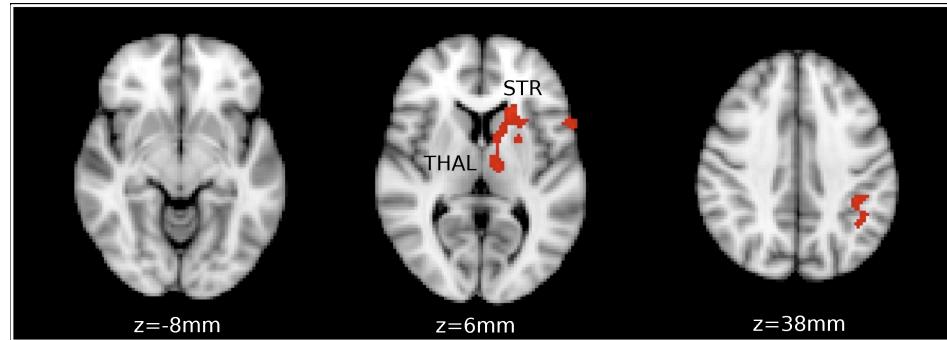
sensorimotor cortices, both for mixed-effects analysis (Figure 4.12) and for fixed-effects analysis (Figure 4.13).

Fig. 4.11: Differences in heat-evoked brain activation between responders and non-responders at baseline



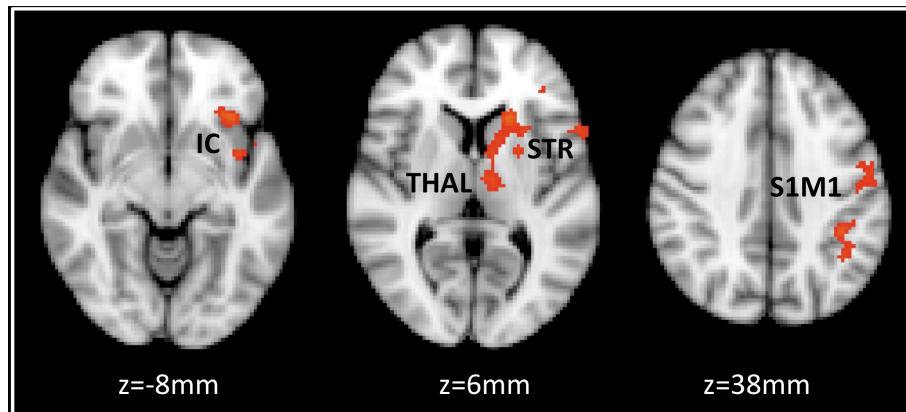
Differences in heat-evoked brain activation at baseline between responders and non-responders. Fixed-effects analysis, $Z > 2.3, p < 0.05, \text{responders} > \text{non-responders}$ contrast. Significant clusters were located in the ipsilateral (right) anterior insular cortex, and bilaterally in the temporal poles.

Fig. 4.12: Differences in changes in heat-evoked brain activation between responders and non-responders



Differences between responders and non-responders in changes in the heat-evoked brain activation after treatment; *responders > non-responders* contrast. Mixed-effects analysis, $Z > 2.3, p < 0.05$. Significant clusters were located contralaterally in the striatum (STR) and the thalamus (THAL).

Fig. 4.13: Differences in changes in heat-evoked brain activation between responders and non-responders



Differences between responders and non-responders in changes in the heat-evoked brain activation after treatment; *responders > non-responders* contrast. Fixed-effects analysis, $Z > 2.3, p < 0.05$. Significant clusters were located contralaterally in the anterior insular cortex (IC), the striatum (STR), the thalamus (THAL), and the primary somatosensory and motor cortices (S1M1).

4.5 Discussion

The aim of this chapter was to analyse changes in pain processing at 2–4 weeks after the start of anti-TNF treatment.

4.5.1 Interactions between changes in clinical, psychological and psychophysical data

We observed a significant reduction in all measured variables, clinical, psychological and psychophysical within the first four weeks after the beginning of anti-TNF treatment.

Improvement of clinical status was consistent with the results of clinical studies on anti-TNF treatment which demonstrated a decrease in pain intensity, disease activity, joint stiffness, swollen and tender joint count, and inflammatory markers within the first month of treatment (Weinblatt et al., 1999; Maini et al., 1999; Elliott et al., 1994; Feldmann et al., 1996; Elliott et al., 1993; Maini and Feldmann, 2002).

A reduction in depressive symptoms after anti-TNF therapy has been reported previously in psoriasis (Tyring et al., 2006; Gelfand et al., 2008), in Crohn's disease (Loftus et al., 2008; Persoons et al., 2005), and in cancer (Tookman et al., 2008). This effect is probably related to reduction of inflammation and may not be specific to anti-TNF; it has been reported after treatment with Adalimumab and Methotrexate as well as just with Methotrexate (Kimel et al., 2008). Most of these studies had longer observation periods, but in a study by Persoons and colleagues a decrease in severity of depressive symptoms was observed within the first four weeks of treatment (Persoons et al., 2005). If reduction of inflammation is the linking factor between disease activity score, daily pain intensity, and depression, this would explain why changes in these variables were correlated. Inflammation, measured with ESR, has the greatest effect on the disease activity score (Maekinen et al., 2007). It has been demonstrated that a severity of depressive symptoms correlates with levels of inflammatory markers (Kop et al., 2002; Panagiotakos et al., 2004) as well as with levels of TNF (Raison et al., 2006; Tyring et al., 2006). Also an analgesic

effect of anti-TNF therapy is mainly a result of suppression of inflammation (Feldmann, 2002).

Some of the mechanisms leading to reduction of depression may be TNF-specific. A neutralisation of TNF may affect mood by changing serotonin transmission and metabolism, because TNF stimulates serotonin uptake (Zhu et al., 2006), and activates serotonin-degrading enzyme: indolamine-2,3-dioxygenase (Robinson et al., 2006). Blocking the pro-inflammatory cytokine cascade may also affect mood indirectly, by reducing sickness-related behaviour (Hayley et al., 1999; Kent et al., 1996). Moreover, it has been demonstrated that clinical pain and depressive symptoms are correlated (Schieir et al., 2009; Dickens et al., 2002) and the interactions work in both directions (Newman and Mulligan, 2000). A decrease in pain intensity may cause a further decrease of depression, as depression in RA is mainly an effect of pain and physical disability (Covic et al., 2006). On the other hand, a reduction in depression is associated with a reduction in pain intensity (Wolfe and Hawley, 1993; Wright et al., 1998; Lin et al., 2003).

In our study, results of the factor analysis demonstrated that there is an association between changes in pain and in depression and catastrophising. This is in line with a study by Keefe and colleagues (Keefe et al., 2004a) who demonstrated that in osteoarthritis changes in catastrophising take place together with changes in depressed mood. Helplessness, the main component of catastrophising, has a strong impact on pain and depression in RA (Covic et al., 2003), and it probably affects depression indirectly through passive coping and pain (Schoenfeld-Smith et al., 1996; Smith et al., 1990). In our study, depression loaded almost equally on the first factor, with changes in pain and psychological scores, and on the second factor, together with a reduction in inflammation. This is consistent with the sickness-behaviour hypothesis, i.e., that the depressive symptoms are related to inflammation.

Taken together, these results suggest that improvement after anti-TNF treatment is a result of a decrease of inflammation, as well as of pain and depression, and those changes are interrelated and enhance one another, with inflammation being the key factor.

4.5.2 Improvement and response

In our study, twelve of twenty three patients showed an improvement at the short-term visit. An improvement was defined as a decrease in disease activity score by at least 1.2 (van Riel and van Gestel, 2000). A simplified criterion was used, i.e., change in the disease activity but not the change in score, as it encompasses those patients who achieved good and moderate EULAR response. This approach was used previously by Pocock and colleagues (Pocock et al., 2008).

At three months, eighteen patients were classified by their consultants as responders. Five patients did not respond and had their anti-TNF drug switched to a different one.

The response to anti-TNF is variable. The results of clinical studies suggest that about 25–40% of patients do not respond to biological DMARDs (Hyrich et al., 2007; Kievit et al., 2009). Currently, there are no biomarkers that can reliably predict a response. In our study, none of the clinical or psychological measures at the baseline differentiated patients who showed improvement at the short-term visit and those who did not. There was also no difference between responders and non-responders except for a higher tender joint count at the baseline and at the short-term visit. These results are in line with a study by Hyrich and colleagues (Hyrich et al., 2006b), who reported that age, gender, disease duration, disease activity, and ESR are not predictive of response. In a study by Brooks (Brooks, 1993), more than 20 affected joints was a predictor of poor response. Other studies have suggested that responders tend to have a shorter disease duration, as it may be associated with more reversible changes (Baumgartner et al., 2004; Smolen et al., 2007); however in our study, we did not see an effect of disease duration on a response or improvement, even after the age effect had been regressed out. A higher baseline DAS28, a higher level of tissue inflammation and levels of inflammatory markers have been also linked with a better response (Wijbrandts et al., 2008; Kievit et al., 2009). This effect was not observed in our study, but this may be caused by two factors: a small sample size³, and a very high disease activity in all our patients.

³ There were 143 patients in the study by Wijbrands et al. and 539 in the study by Kievit et al.

It has been suggested that men tend to have a better response than women (Kvien et al., 2006; Mancarella et al., 2007); however, in our study, the sample was too small to assess the effect of gender. The response to treatment may be also determined by gene polymorphism (Feldmann, 2002), as has been recently demonstrated for Adalimumab (Miceli-Richard et al., 2008). Moreover, depression is a known risk factor for poor response to treatment in general, not just anti-TNF (Bair et al., 2003); it has an effect on recovery in RA (Hamilton et al., 2005); however, in our study only two patients who were depressed completed the short-term visit, which is not sufficient for analysis.

4.5.3 Imaging data

4.5.3.1 Effect of treatment on pressure-evoked pain

When the data of all 23 patients were analysed, there was no significant change in pain-evoked brain activation, despite a reduction in clinical and psychophysical measures. This may be due to the fact that changes in brain activation were small, and the variability between patients was large. It has been suggested by Derbyshire (Derbyshire, 1999) that a reduced response to noxious stimulation in pain patients is related to a high variability of pain-evoked brain activation. In our study, the degree of clinical response also varied in the patients, so the properties of the pressure stimuli at the short-term visit could have been different across patients. It is also possible that, as the effect of the anti-TNF treatment is complex; therefore, the changes in brain activation may not be straightforward, and may not result in a consistent activation map. Moreover, there may be a difference in clinical state and ongoing pain processing, rather than in evoked pain processing. Finally, it is also possible that at the short-term visit there was no change in intensity of the evoked pain, and the differences in pain ratings were related to pain report.

As this study was not blinded, we could not control for placebo effects. However, it has been demonstrated by other authors that when pain is expected to decrease, there is a reduction in activation in pain-related brain regions (Lorenz et al., 2005; Wager et al.,

2004). In our study, there was no change in pain-evoked brain activation, which is an argument against placebo effects.

4.5.3.2 Effect of treatment on heat-evoked pain

For the heat-evoked brain activation, there was a significant difference between the baseline and the short-term visit in the precuneus and the posterior cingulate cortex.

Activation in the posterior cingulate cortex have been reported in neuropathic pain (Hsieh et al., 1995), in a capsaicin hyperalgesia model (Zambreanu et al., 2005), as well as in animal models of chronic pain (Paulson et al., 2002). In a study on heat pain in lower back pain, patients activated this region more than controls (Derbyshire et al., 2002). Therefore, it has been suggested that the posterior cingulate is involved in pain processing in chronic pain states (Derbyshire et al., 2002). In a healthy volunteer study, activation in the medial parietal cortex correlated negatively with pain ratings (Porro et al., 1998). A decrease in cerebral blood flow in the posterior cingulate cortex has been described in response to acute heat pain in healthy volunteers (Vogt et al., 1996). Vogt suggested that the posterior cingulate cortex is not involved in nociception but rather it processes the self-relevance and valence of stimuli (Vogt, 2005), i.e., whether the stimuli are threatening to one's integrity (Price, 2000).

The medial parietal cortex is also involved in attention (Behrmann et al., 2004), and it has been demonstrated that attention is impaired in RA (Dick et al., 2002).

The precuneus and posterior cingulate cortex, together with the medial prefrontal, and ventral anterior cingulate cortices belong to the default mode network (Raichle et al., 2001; Cavanna and Trimble, 2006). These regions have a high metabolic activity during rest, which is reduced during cognitively demanding tasks; this suppression of activity is observed in fMRI results as deactivation (Raichle et al., 2001). However, a reduced deactivation in the default mode network has been reported in chronic pain patients (Baliki et al., 2008). If the observed signal change in our study was related to the default mode network, we would expect that after the treatment the signal change would normalise, i.e., there would be a stronger deactivation, but the opposite effect was observed. There-

fore, we suggest that the increase of activation observed in the medial parietal cortex at the short-term visit was related to changes in attention and self-referential processing in the context of chronic pain, rather than changes in the default mode network.

4.5.4 Improvement and response

Brain activation in response to evoked pain at the baseline and changes in pain-evoked activation did not differentiate between patients who did and those who did not improve; however, there was a difference between patients classified as responders and those classified as non-responders at three months.

For the pressure-evoked pain at baseline, there was more extensive activation in the responders group in the hippocampus. When the fixed-effects analysis was used differences were also observed in the amygdala and the insular cortex. Non-responders showed more activation in the medial prefrontal cortex, i.e., a region involved in appraisal and attention to emotional stimuli, as well as pain modulation (Kalisch et al., 2006; Gracely et al., 2004; Apkarian et al., 2005). This effect was observed only for the fixed-effects analysis; therefore, it cannot be generalised to all the patients.

The differences in pressure-evoked activation changes after treatment were observed only for the fixed-effects analysis. These effect was observed in similar regions as the difference in the baseline activation, namely in the hippocampus, the insular cortex, as well as the thalamus and striatum, and for the opposite contrast in the medial prefrontal cortex.

For the heat-evoked brain activation at the baseline visit, differences were observed only for the fixed-effects analysis. There was a more extensive activation in the responders group in the ipsilateral insular cortex and bilaterally in the temporal cortices. There was no difference for the opposite contrast.

The change in activation to heat between the baseline and the short-term visit in the responders group was observed in the contralateral thalamus and striatum. When a fixed-effects analysis was used, differences were also present in the insular cortex, the primary sensory and primary motor cortex.

The amygdala and hippocampus are activated in response to pain (Derbyshire et al., 1997; Bingel et al., 2002). Some studies reported activation in the amygdala during noxious stimulation (Bingel et al., 2002), whereas others observed deactivation (Becerra et al., 1999; Derbyshire et al., 1997), and it has been suggested that the response depends on the type of the experiment (Bonaz et al., 2002). The amygdala plays an important role in processing the subjective component of pain such as the emotional valence of stimuli (Schneider et al., 2001; Bingel et al., 2002; Bornhovd et al., 2002). It is usually activated by unpleasant stimuli, such as ischaemic pain (Schneider et al., 2001), rectal balloon distension (Wilder-Smith et al., 2004). The amygdala is also involved in interactions between pain and emotions such as fear or stress (Bingel et al., 2002; Neugebauer et al., 2004), and in orienting towards motivationally salient stimuli (Baxter and Murray, 2002; LeDoux, 2003). Furthermore, the amygdala projects to periaqueductal grey and rostral-ventral medulla, and it is involved in descending pain modulation, both enhancement and inhibition (Neugebauer et al., 2004; Bingel et al., 2002; Fields, 2000; Suzuki et al., 2004). Therefore, a decrease in activation in the amygdala in the responders group may reflect a reduction in subjective perception of pain, as well as changes in pain modulation.

Interestingly, amygdala is involved in pain behaviour in rodent arthritis model (Neugebauer and Li, 2003), and changes in this region have been described in chronic pain (Li and Neugebauer, 2004; Bird et al., 2005; Mao et al., 1993). A decrease of activation in the amygdala may be related to a decrease of pain behaviour after treatment (Neugebauer et al., 2004). Moreover, Neugebauer and Li (Neugebauer and Li, 2003) have observed that prolonged pain in the arthritic pain model is associated with an increased response of neurons in the amygdala in response to mechanical but not heat pain. This might explain why we observed changes in this region only for the pressure pain condition.

The amygdala and the hippocampus are involved in mediating the effect of cytokines on mood. Cytokines signal to the central nervous system through the sensory afferents of the vagus nerve, which communicate with neurons within the central nervous system; mainly in the brainstem and the amygdala (Kuhlmann et al., 2009; Dantzer et al., 2008). Cytokines can also signal via the humoral pathways (Dantzer et al., 2008). TNF elicits sickness behaviour, including hyperalgesia and depressed mood, in a dose-dependent

fashion (Hayley et al., 1999; Kent et al., 1996), and TNF inhibition blocks these effects (Watkins et al., 1994b). TNF may affect not only mood but also cognition and behaviour either directly or through its effect of activation of the hypothalamic-pituitary-adrenal axis (Besedovsky et al., 1991; Reichenberg et al., 2001). An inhibition of TNF blocks activation of the hypothalamic-pituitary-adrenal axis (Ebisui et al., 1994). The amygdala regulates hypothalamic-pituitary-adrenal axis (Weidenfeld et al., 2002; Bhatnagar et al., 2004). The amygdala and the hippocampus are also involved in cytokine-induced depressive symptoms (Frenois et al., 2007), and depression in fibromyalgia patients (Giesecke et al., 2005). Therefore, we suggest that the amygdala and the hippocampus are the key regions for the interactions between the anti-TNF treatment and changes in pain and depression.

The amygdala is also involved in learning and conditioning (Buchel et al., 1998), and together with hippocampus these regions take part in novelty encoding, including novelty of pain (Bingel et al., 2002; Grunwald and Kurthen, 2006; Bornhovd et al., 2002). The hippocampus is also activated during uncertainty conditions, an incongruence between expected and experienced pain, as well as during anxiety-induced hyperalgesia (Ploghaus et al., 2000). The reduction of activation in the amygdala and hippocampus observed in our study may be related to conditioning or reduction in anxiety related to order effect (patients were scanner naive at baseline and familiar with the procedures at the next visits). The effect was not observed for any of the conditions for the baseline versus short-term visit contrast; however, the effect may be too small to be observed in the whole-brain analysis. However, the fact that the change in activation in these regions was observed for the contrast between responders and non-responders would suggest that these regions are involved in additional processes related to a treatment response.

The insular cortex is one of the key regions involved in pain processing. The posterior insular cortex is involved in the sensory-discriminative component of pain, whereas the anterior insular cortex encodes the affective dimension of pain experience (Brooks et al., 2002; Craig et al., 2000; Brooks et al., 2005). The anterior insular cortex is also related to autonomic function (Mesulam and Mufson, 1982), homeostatic input and interoception (Craig, 2003a, 2002, 2004; Critchley et al., 2004). The anterior cingulate and insular cortices enhance pain behavioural response to injury or inflammation in persistent pain states

(Bolay and Moskowitz, 2002). In our study, change in activation in the insular cortex correlated with the factor reflecting the change in inflammation.

Changes in the activation were also present in the thalamus and striatum. The thalamus is the main relay centre for the pathways transmitting nociceptive information. Thalamic activation is typically either contralateral to stimulation or bilateral (Casey et al., 1996). Ipsilateral activation in the thalamus reflects probably an input from the brainstem (Millan, 1999). The striatum is involved in the sensory-discriminative as well as affective, and cognitive dimensions of pain. It is also important for modulation of the nociceptive information (Chudler and Dong, 1995; Bingel et al., 2004). A larger decrease of activation in these regions in responders may reflect larger decrease of nociceptive input in this group.

Taken together, these results suggest that the observed changes in the amygdala, the hippocampus, and the insular cortex reflect the effect of anti-TNF treatment on clinical status, including behaviour and pain. We suggest that this reflects changes in nociceptive transmission related to the effect of treatment on pain modulation. It is also likely that anti-TNF treatment affects mainly the neuronal circuits controlled by the amygdala and the hippocampus.

4.6 Main findings

- There was a significant decrease in clinical, psychological and psychophysical measures within the first four weeks after the beginning of the treatment.
- None of the clinical or psychological measures at the baseline differentiated patients who did and did not respond.
- There was a higher tender joint count in the non-responders group.
- For the pressure pain condition, there was more activation in the amygdala, the hippocampus, and the insular cortex in the responders group, and in the medial prefrontal cortex in non-responders
- For the heat-evoked brain activation, the differences in brain activation changes after treatment were present in the contralateral thalamus, striatum, and the insular cortex.

Chapter 5

LONG-TERM EFFECTS OF ANTI-TNF TREATMENT

5.1 Introduction

In the previous chapter, we demonstrated that there were changes in the pain-evoked brain activation within the first four weeks after the beginning of the anti-TNF treatment. In this chapter, we wanted to investigate changes in the pain-evoked activation at six months after the start of the treatment, when the full effect of the medication was present, and the disease activity was stable (Kievit et al., 2009). We were also interested whether the brain activation pattern after treatment was similar to the activation in healthy controls.

5.2 Aims and hypotheses

The aim of this chapter was to assess changes in central processing of noxious pressure and heat stimuli by RA patients at six months after the start of anti-TNF treatment. We were interested whether the psychological scores and brain activation "normalise" after the treatment.

5.3 Methods

5.3.1 Participants

We analysed data of RA patients who were classified as responders by their consultants at three months after the start of anti-TNF therapy, and who completed all three visits: baseline PAT_{BL} , short-term, PAT_{ST} , and long-term PAT_{LT} , i.e., we analysed data only from the patients who had responded to treatment and continued the therapy for over six months. We compared the patients' data with data of fourteen healthy controls, who completed the baseline visit CON_{BL} and the follow-up CON_{FU} visit at six months.

Patients

There were fifteen patients who responded to the medication, and completed all three visits.¹ The median age in this group was 64.0 years (IQR 18.0), and the median disease duration was 17.0 years (IQR 16.0). There were eleven female patients and four male patients. One patient was diagnosed with depression (i.e., clinical depression at the time of the study) and was treated with Amitriptyline.

Patients were receiving all three anti-TNF drugs, alone or in combination with Methotrexate: Etanercept ($n = 5$), Adalimumab ($n = 4$), Etanercept with Methotrexate ($n = 3$), Adalimumab with Methotrexate ($n = 1$), and Infliximab with Methotrexate ($n = 2$). The median time between the baseline and the second visit was 18.0 days (IQR 7.0), and between the baseline and the long-term visit was 6 months (IQR 4).

Twelve patients refrained from taking painkillers at all three visits, one took painkillers at all three visits, and two did take analgesics at the baseline, but not at the subsequent visits. One patient stopped taking painkillers after the baseline visit, and one stopped after the short-term visit.

¹ 23 patients attended the short-term visit, and 15 of them completed the short-term and the long-term visit. Five patients did not respond to the treatment and had the medication changed before the long-term visit. Three patients did not attend the long-term visit. Thirteen patients completed only the baseline visit: nine did not return for the subsequent scans (four patients dropped out, five were missed due to a gap in the study), three did not begin the treatment, and one was allergic to the treatment.

Two patients had their DMARDs changed between the baseline and the long-term visit: one had a dose of Leflunomide reduced, and one had Leflunomide stopped.

Controls

Fourteen control subjects completed the baseline visit CON_{BL} and the follow-up visit CON_{FU} . The median age in this group was 59.0 years (IQR 20.0); there were thirteen women and one man.

There was no difference in age between patients and controls (the Mann–Whitney U test (2-tailed) $p = 0.192$). There were more women in the control group but the sample was not sufficient for a statistical analysis.

Matched patients and controls

It has been demonstrated in Chapter 3 that the patient-control pairs approach is more sensitive to differences between patients and controls; therefore, we compared a subset of eleven patients at six months, PAT_{LT} and eleven matched controls at the baseline CON_{BL} .

An analysis between the follow-up data in both groups, i.e., PAT_{LT} and CON_{FU} , would have been more appropriate; however, there were only five controls in the matched control group who completed the follow-up visit.

In the group of matched eleven patients, the median age was 60 years (IQR 17), and there were seven women and four men. In the group of eleven matched controls, the median age was 61 years (IQR 6), and the gender ratio was the same as in the patient group.

5.3.2 Experimental protocol

The pre-scanning assessment and scanning protocol were described in detail in the Methods chapter in subsections 2.2.5 and 2.2.6.

5.3.3 Analysis of clinical, psychological, and psychophysical data

5.3.3.1 Overall treatment effects

Changes in clinical, psychological, and psychophysical scores across all three visits were assessed using the Friedman Test for related samples, which is a non-parametric equivalent of the parametric repeated measures analysis of variance.

5.3.3.2 Comparison of short-term and long-term effects of treatment

In this chapter we analysed data only from patients for whom anti-TNF treatment was effective; therefore, we repeated the comparison between the baseline visit PAT_{BL} and the short-term visit PAT_{ST} as well as the comparison between the baseline PAT_{BL} and the long-term visit PAT_{LT} .

The short-term $PAT_{BL} - PAT_{ST}$ and long-term $PAT_{BL} - PAT_{LT}$ effects of the treatment on clinical, psychophysical and psychological measures were analysed using the Wilcoxon Signed Ranks Test.

5.3.3.3 Response and remission

We were interested in the features associated with effects of treatment, such as clinical response and remission. The EULAR criteria were used to define response and remission (van Gestel et al., 1996, 1998). The criteria were described in detail in subsection 2.2.6 of the Methods chapter. A remission was defined as very little disease activity with one or no tender joints and the DAS28 below 2.6 (Makinen et al., 2008; Sokka et al., 2008; Kristensen et al., 2008).

5.3.3.4 Comparison between patients and controls at six months after the baseline visit

To investigate whether the measures in patients at the long-term visit were different from controls, a group comparison was performed between patients' results at the long-term PAT_{LT} visit and the follow-up data from the control group CON_{FU} .

We were interested whether there were any changes related to repeated scanning visits rather than to treatment effects; therefore, we analysed between-visits differences in the control group. We used the Wilcoxon Signed Rank Test (2-tailed) to assess whether there were any changes in measured variables between the baseline CON_{BL} , and the follow-up CON_{FU} visit in the control group.

5.3.4 Analysis of imaging data

5.3.4.1 Overall effects of treatment

Overall effects of the treatment across all three visits were analysed using a two-level analysis. The results of first-level analyses for all fifteen patients for all three visits were entered into the model and data from each visit were modelled as a separate group. The contrast was set as "-1 0 1" to identify regions where activation increased across the visits ($PAT_{BL} < PAT_{ST} < PAT_{LT}$), and "1 0 -1" where activation decreased ($PAT_{BL} > PAT_{ST} > PAT_{LT}$). This analysis was done for pressure and perception-matched heat conditions separately. This model analysed a trend across the visits; however, it did not correct for the fact that the data were acquired in the same group of patients at three different occasions.

5.3.4.2 Differences between the visits

The within-subject difference between visits was analysed using a higher-level analysis with an extended paired t-test, i.e., "tripled t-test". The first-level results for all fifteen patients for all three visits were entered into the model. Data from each visit was modelled as a separate group, and each patient's mean was modelled as an additional re-

gressor of no interest. Contrasts were set for the following comparisons: $PAT_{BL} > PAT_{ST}$, $PAT_{BL} > PAT_{LT}$, and $PAT_{ST} > PAT_{LT}$.

5.3.4.3 Comparison of short-term and long-term effects of anti-TNF treatment

In this chapter, we analysed only data of the patients who responded to the treatment. Therefore, we investigated the short- and long-term effects of treatment for the patients in whom the treatment was effective. A two-sample paired t-test was performed between the first-level results from the baseline and the short-term visit (PAT_{BL-ST}), and between the baseline and long-term session (PAT_{BL-ST}). In this model, the first regressor represented the between-visit difference and other regressors modelled each patient's mean. The analysis was performed for pressure- and heat-evoked pain, separately.

5.3.4.4 Comparison of short-term and long-term effects of anti-TNF treatment

To assess the effect of treatment in the long-term controlling for the possible effect of time, learning, conditioning, and expectations a comparison was performed between changes in patients and controls, i.e., $(PAT_{BL} > PAT_{LT}) > (CON_{BL} > CON_{FU})$. The analysis was performed for pressure- and heat-evoked pain, separately.

5.3.4.5 Comparison between patients and controls at six months

We were interested whether there were any differences in pain-evoked brain activation between the successfully treated patients at six months (n=15) and healthy controls (n=14).

A group comparison was performed between the patients' imaging data at the long-term visit PAT_{LT} and the control data from the follow-up visit CON_{FU} . An unpaired two-sample t-test between the results of the first-level analysis was used. We compared the scans at six months, so that subjects in both groups were familiar with the procedures and stimulation; therefore, partly controlling for expectation, anxiety, learning, and conditioning effects. The analysis was performed for pressure- and heat-evoked pain, separately.

This analysis had the advantage of a relatively large sample size; however, the groups were not optimally matched with respect to age, gender, and stimulation strength. Therefore, this analysis was repeated in the paired data, i.e., in the eleven patients and their age- and gender-matched controls. The analysis was done in patient's data from the long-term visit PAT_{LT} and control's data from the baseline visit CON_{BL} . Controls' data from the baseline visit have been used, because only five controls from the matched group completed the follow-up scan.

To assess reproducibility, controls' data from the baseline CON_{BL} and follow-up visit CON_{FU} were compared using a paired t-test between the results of the first-level analysis. A separate test was performed for each type of stimulation: pressure, heat, and visual.

5.3.4.6 Control task

To control for a possible non-specific drug effect on brain activation, a pre- and post-treatment response to the visual task was compared in the patient group. A paired analysis was performed to estimate possible short- and long-term changes in response to visual stimulation, i.e., for the $PAT_{BL} > PAT_{ST}$ and $PAT_{BL} > PAT_{LT}$ contrast, separately.

5.4 Results

5.4.1 *The effects of treatment on clinical, psychophysical, and psychological data across all three visits in the patient group*

Absolute values of clinical, psychophysical, and psychological measures for all three visits were presented in Table 5.1.

All the measures have changed significantly over the course of treatment (Table 5.2 and Table 5.3 and Figures 5.1 - 5.5). The disease activity score, ESR, daily pain intensity, tender joint count and depression scores decreased significantly between the baseline and the short-term visit ($PAT_{BL} > PAT_{ST}$), as well as between the short-term and long-term visit ($PAT_{ST} > PAT_{LT}$). Pain ratings for pressure and heat pain, swollen joint count

and duration of joint stiffness decreased significantly over the short-term period ($PAT_{BL} > PAT_{ST}$) but the change between the short-term and long-term visit ($PAT_{ST} > PAT_{LT}$) was not significant. The opposite pattern was observed for catastrophising scores (Table 5.3).

Table 5.1: Clinical, psychological, and psychophysical data of the RA patients at each visit

<i>Variable</i>		<i>BL</i>	<i>ST</i>	<i>LT</i>
Disease activity	mean (SD)	6.1 (0.8)	4.8 (0.9)	3.4 (1.2)
Tender joint count	median (IQR)	11.0 (7.0)	10.0 (8.0)	4.0 (8.0)
Swollen joint count	median (IQR)	11.0 (7.0)	8.0 (5.0)	3.0 (5.0)
ESR, $\frac{mm}{h}$	median (IQR)	34.0 (29.0)	23.0 (23.0)	13.0 (11.0)
Daily pain intensity	median (IQR)	6.5 (3.0)	4.0 (3.0)	2.5 (3.5)
Joint stiffness, minutes	median (IQR)	54.7 (45.0)	10.0 (60.0)	0.0 (20.0)
Pressure pain rating	median (IQR)	5.0 (1.1)	3.0 (3.2)	2.0 (3.1)
Heat pain rating	median (IQR)	6.0 (0.5)	5.5 (2.0)	5.5 (2.0)
Depression score	median (IQR)	8.0 (6.0)	6.0 (9.0)	4.0 (5.0)
Catastrophising score	median (IQR)	10.0 (18.0)	11.0 (9.0)	3.0 (5.0)

Absolute values of clinical, psychophysical and psychological measures in the patient group at the baseline (BL), short-term (ST), and long-term (LT) visit. Abbreviations: ESR - erythrocyte sedimentation rate.

Table 5.2: Changes in clinical, psychophysical, and psychological measures across all three visits

<i>Variable</i>	χ^2	<i>P-value</i>
Disease activity	28.13	< 0.0005
Tender joints count	18.53	< 0.0005
Swollen joints count	19.40	< 0.0005
ESR, $\frac{mm}{h}$	24.4	< 0.0005
Daily pain intensity	23.05	< 0.0005
Joint stiffness, minutes	20.94	< 0.0005
Pressure pain rating	19.57	< 0.0005
Heat pain rating	8.68	0.013
Depression score	20.86	< 0.0005
Catastrophising score	16.26	< 0.0005

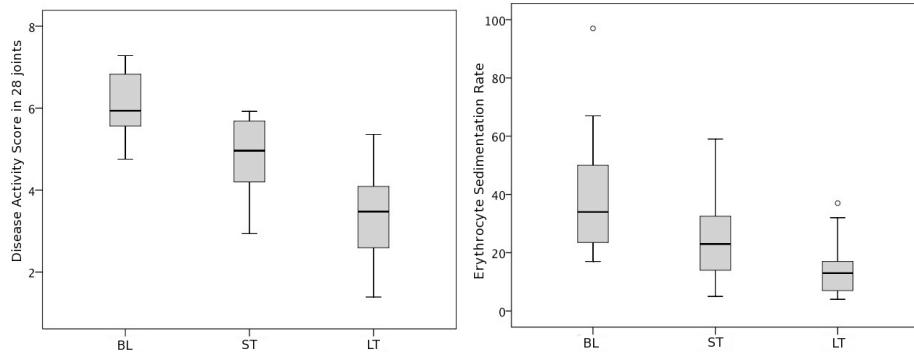
Overall change in clinical, psychophysical and psychological measures in the patient group. The Friedman test. Abbreviations: ESR - erythrocyte sedimentation rate.

Table 5.3: Changes in clinical, psychophysical, and psychological variables between visits

Variable	BL-ST		ST-LT		BL-LT	
	Z-value	P-value	Z-value	P-value	Z-value	P-value
Disease activity	-3.35	0.001	-3.41	0.001	-3.41	0.001
Tender joints count	-2.82	0.005	-3.13	0.002	-3.35	0.001
Swollen joints count	-2.88	0.004	-1.83	0.068	-3.33	0.001
ESR, $\frac{\text{mm}}{\text{h}}$	-2.64	0.008	-3.154	0.002	-3.41	0.001
Daily pain intensity	-2.88	0.004	-3.13	0.002	-3.41	0.001
Joint stiffness, minutes	-2.81	0.005	-1.69	0.091	-3.3	0.001
Pressure pain rating	-3.05	0.002	-1.83	0.068	-3.31	0.001
Heat pain rating	-2.74	0.006	-0.92	0.358	-1.67	0.095
Depression score	-2.28	0.022	-2.23	0.026	-3.19	0.001
Catastrophising score	-1.89	0.058	-2.92	0.003	-2.83	0.005

Changes in clinical, psychophysical and psychological measures between the visits in the patient group. Z and P value of the Wilcoxon Signed Ranks Test. Abbreviations: ESR - erythrocyte sedimentation rate, baseline - BL, short-term - ST, and long-term LT visit.

Fig. 5.1: Treatment effect on disease activity and inflammatory markers



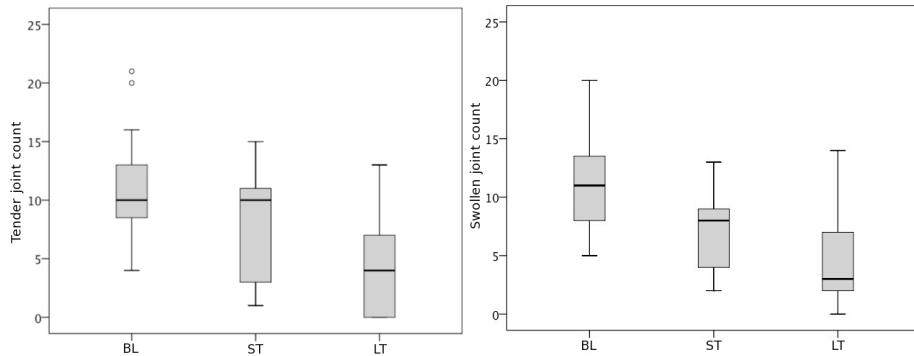
Results, absolute values, of the disease activity score (DAS28) and erythrocyte sedimentation rate (ESR) in the patient group for all three visits. Median values are presented within the 25th and 75th interquartile box, non-outlier maxima and minima (whiskers). o - an outlier $< 3IQR$ above the 75th quartile.

5.4.2 Response and remission

At the short-term visit, eight patients improved, i.e., their disease activity score DAS28 decreased by more than 1.2. Two patients achieved good response, and six achieved moderate response according to the EULAR criteria.

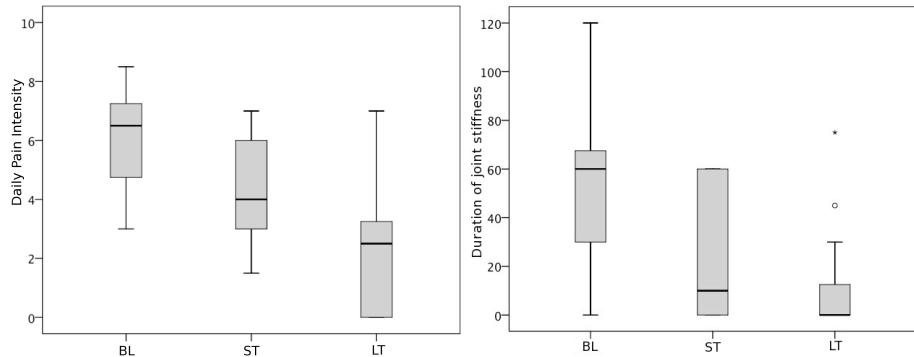
At the long-term visit, all patients improved, i.e., their reduction in disease activity DAS28 decreased by more than 1.2. Six patients achieved a good response, and seven a moderate response according to the EULAR criteria.

Fig. 5.2: Treatment effect on tender and swollen joint count



Results, absolute values, of tender and swollen joint count in the patient group for all three visits. Median values are presented within the 25th and 75th interquartile box, non-outlier maxima and minima (whiskers). o - an outlier $< 3IQR$ above the 75th quartile.

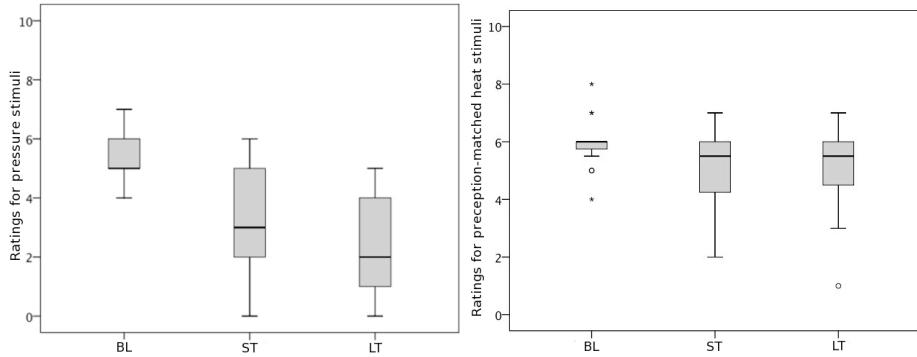
Fig. 5.3: Treatment effect on daily pain intensity and duration of morning joint stiffness



Results, absolute values, of an average intensity of daily pain and duration of joint stiffness on waking in the morning (in minutes) in the patient group for all three visits. Median values are presented within the 25th and 75th interquartile box, non-outlier maxima and minima (whiskers). o - an outlier $< 3IQR$ above the 75th quartile.

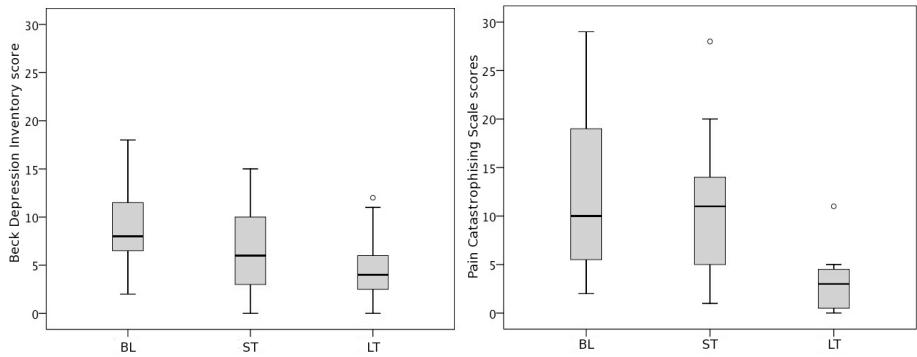
Only four patients achieved remission at the long-term visit, i.e., their disease activity score was below 2.6. These patients had no tender joints at the long-term visit, and the swollen joint count was between one and seven. In the group that achieved remission, one patient was treated with Adalimumab, two with Adalimumab and Methotrexate, and one with Etanercept. Three of these patients were male, their disease activity score and tender joint count at the baseline were lower than in the remaining eleven responders (the Mann-Whitney test, 2-tailed, $p = 0.04$ and $p = 0.001$, respectively). There was no

Fig. 5.4: Treatment effect on pain ratings



Results, absolute values, of pain ratings for pressure and heat pain in the patient group for all three visits. Median values are presented within the 25th and 75th interquartile box, non-outlier maxima and minima (whiskers). o - an outlier $< 3IQR$ above the 75th quartile, and * - an outlier $> 3IQR$ above the 75th quartile.

Fig. 5.5: Treatment effect on depression and catastrophising scores



Results, absolute values, of depression and catastrophising scores in the patient group for all three visits. Median values are presented within the 25th and 75th interquartile box, non-outlier maxima and minima (whiskers). o - an outlier $< 3IQR$ above the 75th quartile.

significant difference in age, disease duration, ESR, and depression scores at the baseline, between the patients that achieved remission and those who did not.

5.4.2.1 Patients after treatment versus controls

To investigate whether scores in the patient group returned within a normal range after the treatment, patients' pain ratings for pressure and heat, as well as the psychological

scores from the long-term visit PAT_{LT} ($n=15$) were compared with the controls' data from the follow-up visit CON_{FU} ($n=14$). After treatment patients rated pressure stimuli lower than at the baseline visit, but higher than controls. Patients and controls rated the heat stimuli as moderately painful, i.e., 6 out of 10. There were no differences in depression or catastrophising scores between patients PAT_{LT} and controls CON_{FU} . The values were summarised in Table 5.4.

As was demonstrated in Chapter 3, age and gender may affect the psychophysical measures, therefore the analysis of pain ratings for pressure and heat pain was repeated in matched groups of eleven patients PAT_{LT} and eleven controls CON_{BL} using the Mann-Whitney U test, but the difference was not significant (Table 5.5).

In the control group, there was no difference in ratings of intensity of pressure and heat stimuli, as well as in the depression and catastrophising score between the baseline CON_{BL} and the follow-up visit CON_{FU} (Table 5.4). This would suggest that there was no difference associated with possible learning effects, conditioning or decrease in anxiety at the follow-up visit in the control group.

Table 5.4: Clinical and psychological measures in patients and controls

Variable	PAT_{LT}	CON_{BL}	CON_{FU}	PAT_{LT} vs. CON_{FU}	CON_{BL} vs. CON_{FU}
	Value	Value	Value	P-value	P-value
Pressure pain rating	2.0 (3.1)	0.0 (0.5)	0.25 (1.0)	0.002	0.305
Perception-matched heat pain rating	5.8 (1.5)	6.0 (1.0)	6.0 (0.8)	0.347	0.339
Depression score	4.0 (5.0)	3.0 (5.0)	2.5 (4.0)	0.377	0.769
Catastrophising score	3.5 (4.0)	5.0 (9.0)	5.5 (11.0)	0.252	0.305

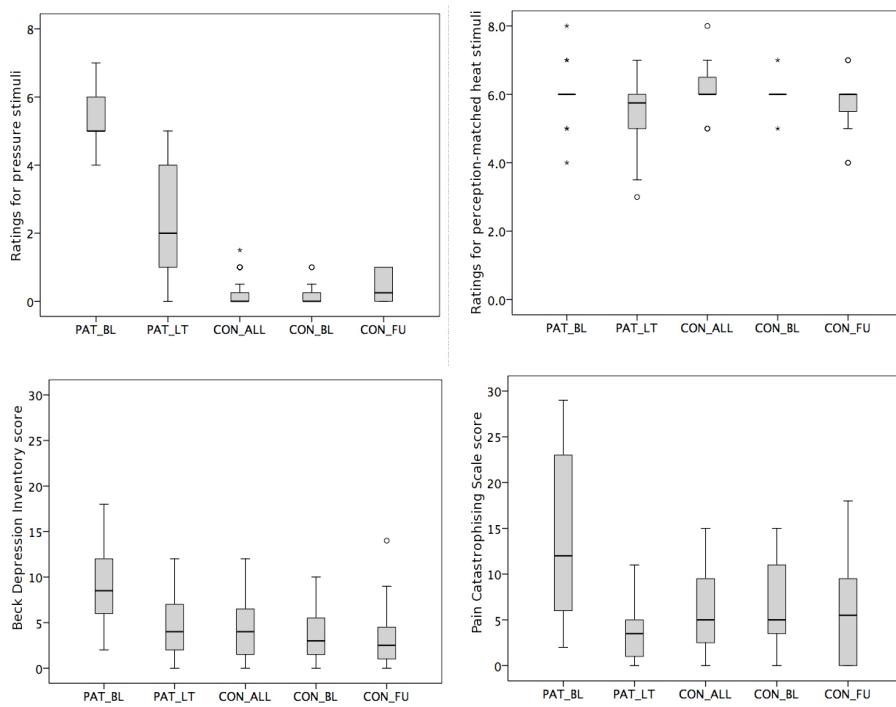
Median values and interquartile range (IQR), and p-value of the Mann-Whitney U test (2-tailed) between patients PAT_{LT} ($n=15$) and controls CON_{FU} ($n=14$), and p-value of the Wilcoxon Signed Rank Test between the baseline CON_{BL} and the follow-up CON_{FU} visit in the control group.

Table 5.5: Clinical and psychological measures in patients and controls, matched data

Variable	PAT_{LT} Value	CON_{BL} Value	PAT_{LT} vs. CON_{BL} P-value
Pressure pain rating	1.5 (3.2)	0.0 (1.0)	0.020
Stimulation-matched heat pain rating	6.0 (2.5)	5.0 (2.0)	0.652
Perception-matched heat pain rating	6.0 (2.5)	5.8 (1.2)	0.717
Depression score	3.0 (3.0)	4.0 (8.0)	0.847
Catastrophising score	3.0 (4.0)	4.0 (6.0)	0.217

Median values and interquartile range (IQR), and p-value of the Mann–Whitney U test (2-tailed) between matched eleven patients PAT_{LT} , and eleven controls CON_{BL} .

Fig. 5.6: Psychological and psychophysical scores in the patient and control group



Results, absolute values for psychological and psychophysical scores in the patient responder group at the baseline PAT_{BL} ($n=15$), patient group at the long-term visit PAT_{LT} ($n=15$), all controls at the baseline CON_{ALL} ($n=26$), and controls who were scanned twice: at the baseline CON_{BL} ($n=14$) and six months later CON_{FU} ($n=14$). Median values are presented within the 25th and 75th interquartile box, non-outlier maxima and minima (whiskers). o - an outlier $< 3IQR$ above the 75th quartile, $*$ - an outlier $> 3IQR$ above the 75th quartile.

5.4.3 Imaging results

5.4.3.1 Treatment effect on pressure pain in the patient group

In the patient group, there was a linear trend for a decrease in activation in response to pressure-evoked pain across all three visits. The significant clusters were located in the following regions: the ipsilateral hippocampus, the ipsilateral amygdala, the contralateral premotor cortex (Figure 5.7). There was no increase of activation with the treatment.

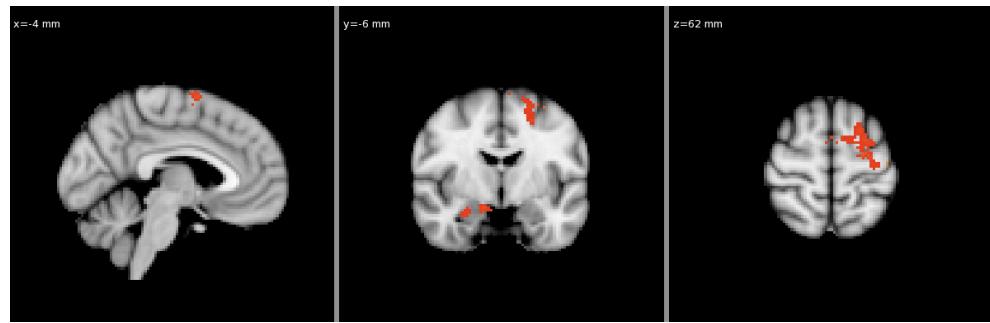
A paired analysis, a tripled two-sample paired t-test, showed significant differences only between the baseline PAT_{BL} and long-term visit PAT_{LT} , but not between the baseline and the short-term visit or between the short-term and long-term visit (Figure 5.8). Significant clusters were located in the ipsilateral amygdala, the ipsilateral hippocampus, the contralateral primary motor, the primary somatosensory cortices, and the premotor cortex.

In the previous chapter, we demonstrated that there was no change in activation in response to pressure between the baseline PAT_{BL} and short-term visit PAT_{ST} in a group consisting of responders and non-responders. In this chapter, only the data of 15 responders were used for the analysis. Over the short term, there was a decrease in activation in the contralateral primary somatosensory and the primary motor cortices (Figure 5.9). Over the long term, there was a decrease in activation in the primary somatosensory and the primary motor cortices as well as in the contralateral premotor cortex, the supplementary motor area, the contralateral insular cortex and the operculum, the ipsilateral hippocampus, and the ipsilateral amygdala (Figure 5.10), i.e., in the same areas as in the tripled t-test (Figure 5.8) but additionally including the insular cortex. There was a decrease in signal in the contralateral posterior insular cortex for the pressure condition (Figure 5.12), however, the effect might have been too small to be significant in analyses other than direct comparison between the baseline PAT_{BL} and the long-term condition PAT_{LT} .

To control for learning effects related to repeated scans, an additional analysis was performed, in which the difference in brain activation between the visits in the control group was subtracted from the difference in brain activation in the patient group, i.e.,

$(PAT_{BL} > PAT_{LT}) > (CON_{BL} > CON_{FU})$. For the pressure condition, significant clusters were located bilaterally in the amygdala, the hippocampus, the thalamus, the insular cortex, the striatum (the ventral putamen), the anterior cingulate cortex, the supplementary motor area, the nucleus reticularis cuneiformis, the periaqueductal grey, in the contralateral primary motor and somatosensory cortices, and the contralateral red nucleus (Figure 5.11).

Fig. 5.7: Treatment effect on pressure pain across all three visits



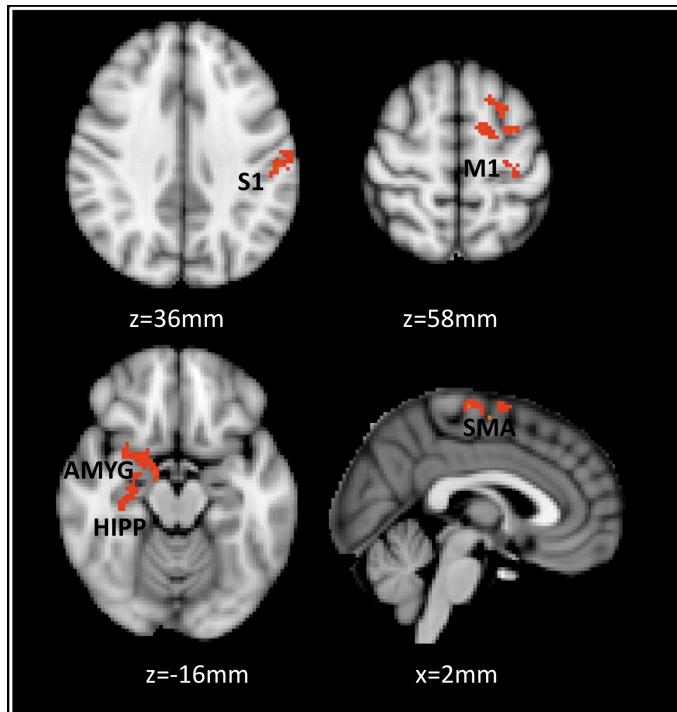
Changes in the pressure evoked activation with treatment; a linear trend across all three visits. Mixed-effects analysis, $Z > 2.3, p < 0.05$. A decrease of activation in the ipsilateral hippocampus, the ipsilateral amygdala, the contralateral premotor cortex, and the supplementary motor area.

5.4.3.2 Treatment effect on heat pain in the patient group

For the heat condition in the patient group across all three visits (a linear trend), there was a change in activation in the precuneus, the posterior cingulate cortex, the contralateral insular cortex, the operculum, and the premotor cortex (Figure 5.13). There was no decrease in activation across the visits.

There were no differences between visits when the analysis was controlled for repeated measures, i.e., a tripled t-test. When a two-sample paired t-test was used to compare the activation at the baseline PAT_{BL} and at the short-term visit PAT_{ST} there was an increase of activation in the precuneus (Figure 5.16). Between the baseline PAT_{BL} and the long-term visit PAT_{LT} there was an increase in activation in the precuneus as well as in the contralateral insular cortex and operculum (Figure 5.17).

Fig. 5.8: Treatment effect on pressure pain, a tripled t-test

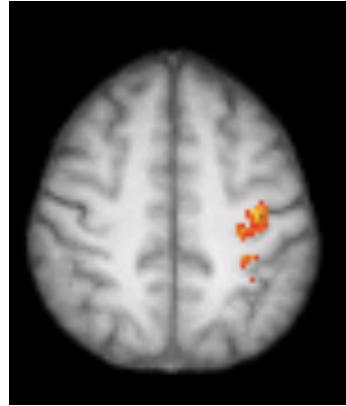


Treatment effect on response to pressure pain. A tripled t-test, i.e., paired analysis of differences between all three visits. Mixed-effects analysis, $Z > 2.3, p < 0.05$. There were significant differences only for the $PAT_{BL} > PAT_{LT}$ contrast. The significant clusters were located in the contralateral premotor cortex, primary somatosensory and primary motor cortex (S1M1), in the ipsilateral amygdala (AMYG), the ipsilateral hippocampus (HIPP), and bilateral supplementary motor area (SMA).

When the learning effect was controlled for, i.e., $(PAT_{BL} > PAT_{LT}) > (CON_{BL} > CON_{FU})$, differences were observed in the posterior cingulate cortex, the precuneus and the lingual gyrus (Figure 5.18).

To further investigate the changes in heat-evoked brain activation, a percentage signal change in patients and controls was analysed in the precuneus and the contralateral insular cortex (Figure 5.14 and Figure 5.15). The precuneus mask was created from the Harvard-Oxford Cortical Structural Atlas region thresholded at 20% as the clusters in the precuneus were not consistent between the results. The posterior insular cortex mask was created from the cluster in the insular cortex from the activation map in Figure 5.13.

Fig. 5.9: Treatment effect on pressure pain at the short-term visit



Treatment effect at the short-term on response to pressure pain. Paired t-test, baseline versus short-term effect visit, $PAT_{BL} > PAT_{ST}$ contrast. Mixed-effects analysis, $Z > 2.3, p < 0.05$. Significant cluster was located in the contralateral primary somatosensory and primary motor cortices.

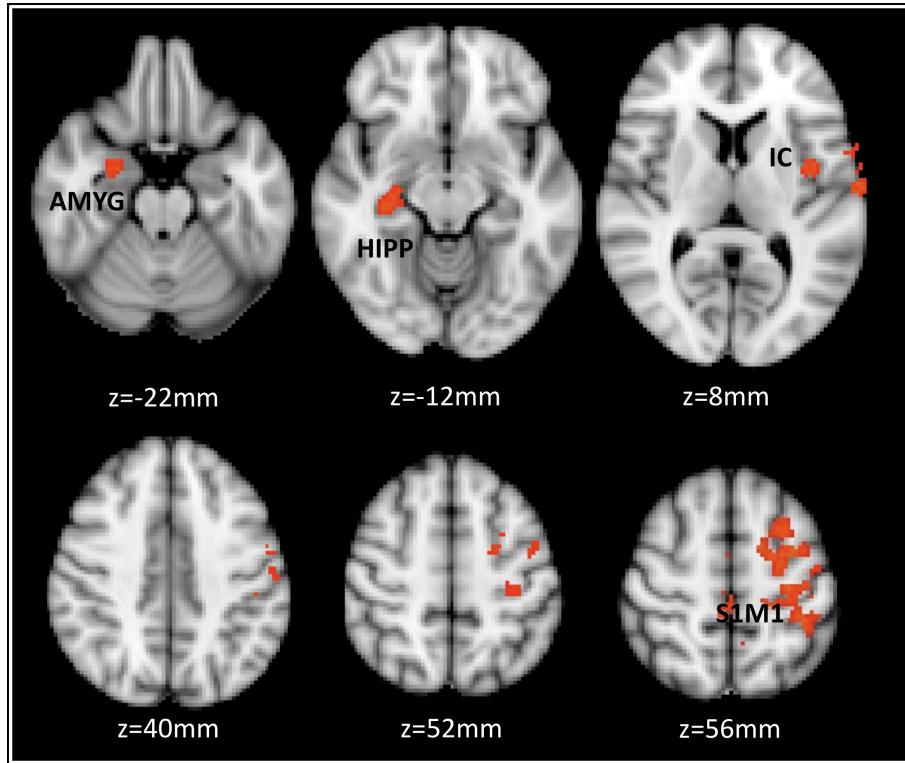
5.4.3.3 Visual task

There was no difference in activation in response to the visual task between any of the visits.

5.4.3.4 Comparison between patients and controls six months after the baseline visit

When the long-term data in the patient group PAT_{LT} ($n=15$) were compared with the control data from the follow-up visit CON_{FU} using an unpaired t-test, there was no group difference for pressure, perception-matched heat and stimulation-matched heat conditions. The analysis was repeated in the matched subset of subjects, i.e., eleven patients PAT_{LT} , and eleven age- and gender-matched controls CON_{BL} , who received stimuli of the same intensity during the pressure and stimulation-matched heat condition. There was more activation in the patient group in response to pressure, which is consistent with the psychophysical data. The significant clusters were located mainly in the regions involved in encoding unpleasantness of stimuli such as the anterior insular cortices, the anterior cingulate cortex, the medial thalamus, withdrawal such as the supplementary motor area, and the midbrain (Figure 5.19). There was no difference in brain activation

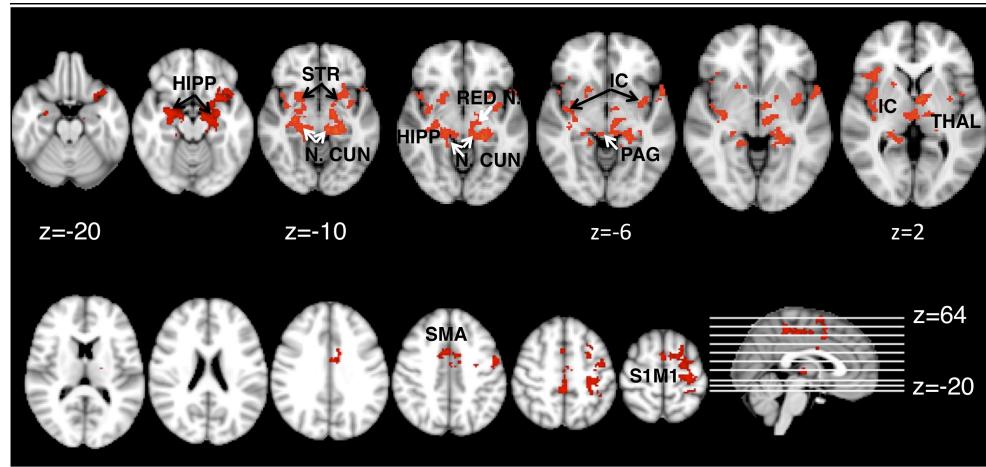
Fig. 5.10: Treatment effect on pressure pain at the long-term visit



Treatment effect on response to pressure pain. A paired t-test between baseline and long-term visit, $PAT_{BL} > PAT_{LT}$ contrast. Mixed-effects analysis, $Z > 2.3, p < 0.05$. The significant clusters were located in the bilateral premotor cortex, the contralateral insular cortex (IC), the ipsilateral hippocampus (HIPP), and primary somatosensory and primary motor cortex (S1M1).

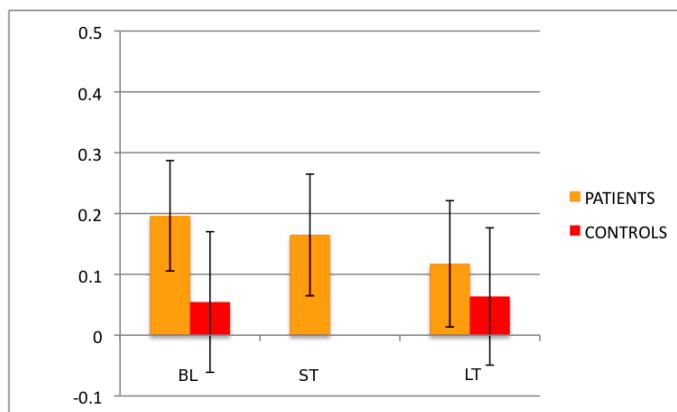
in response to perception- or stimulation-matched heat in the patient and control group. This suggests that the pain processing normalises in patients who respond to treatment.

Fig. 5.11: Changes in pressure-evoked activation in patients controlling for learning effects



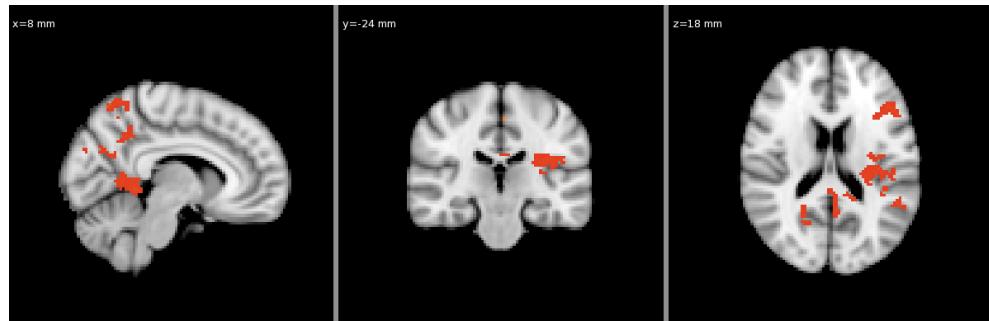
Treatment effect on response to pressure pain, long-term controlled for learning effects. A two-sample unpaired t-test, ($PAT_{BL} > PAT_{LT} > (CON_{BL}) > CON_{FU}$). Mixed-effects analysis, $Z > 2.3, p < 0.05$. Differences observed bilaterally in the hippocampus (HIPP), the nucleus reticularis cuneiformis (N. CUN.), the insular cortex (IC), the striatum (STR), the thalamus (THAL), the supplementary motor area (SMA), and the contralateral primary somatosensory and motor cortices (S1M1), the periaqueductal grey matter (PAG) and contralateral red nucleus (RED N.).

Fig. 5.12: Percentage signal change in response to pressure-evoked pain in the posterior insular cortex



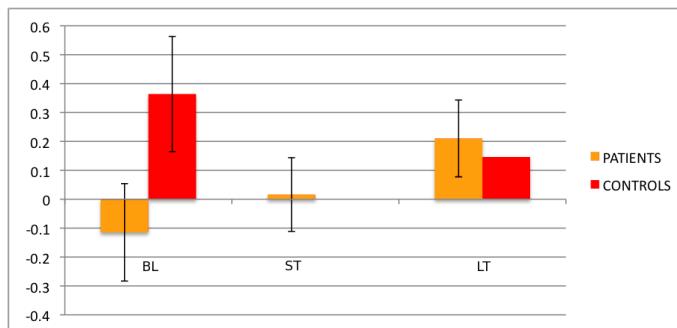
A plot of percentage signal change in response to pressure-evoked pain in the contralateral posterior insular cortex cluster from the Figure 5.13. A mean values for all three visits in the patient group and the baseline and the follow-up visit in the control group. (A cluster was chosen rather than a mask as the insular atlas mask is large whereas the each part of the insular cortex fulfils different functions. Moreover, we wanted to compare changes in activation in the insular cortex for the pressure and heat-pain condition. See also Figure 5.15.)

Fig. 5.13: Treatment effect on heat pain across all three visits



A treatment effect on thermal pain across all three visits. Regions that showed a linear trend throughout all three visits. Mixed-effects analysis, $Z > 2.3, p < 0.05$. An increase of activation in the precuneus, the posterior cingulate cortex, the contralateral insular cortex, and the operculum.

Fig. 5.14: Percentage signal change in response to heat-evoked pain in the precuneus



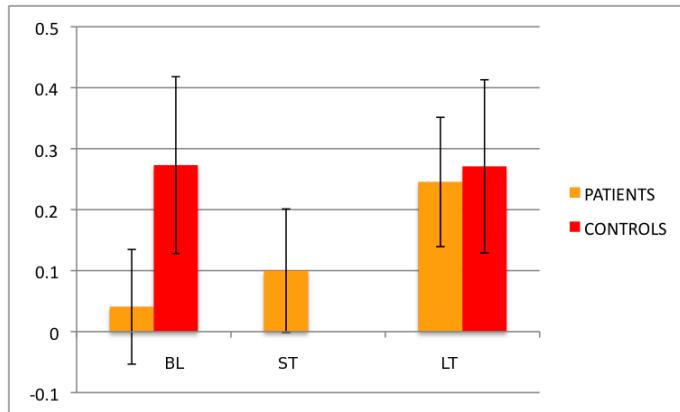
Treatment effect on thermal pain across all three visits, a plot of percentage signal change in the precuneus atlas mask. Mean values for all three visits in the patient group and the baseline and the follow-up visit in the control group.

5.5 Discussion

5.5.1 Effects of anti-TNF treatment on clinical and psychophysical measures

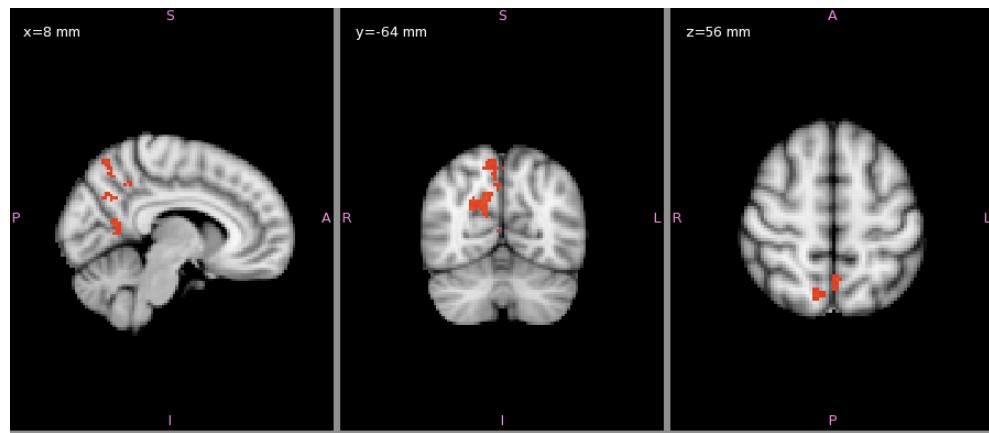
In this chapter, we investigated long-term effects of the anti-TNF treatment on pain processing in RA.

Fig. 5.15: Percentage signal change in response to heat-evoked pain in the posterior insular cortex



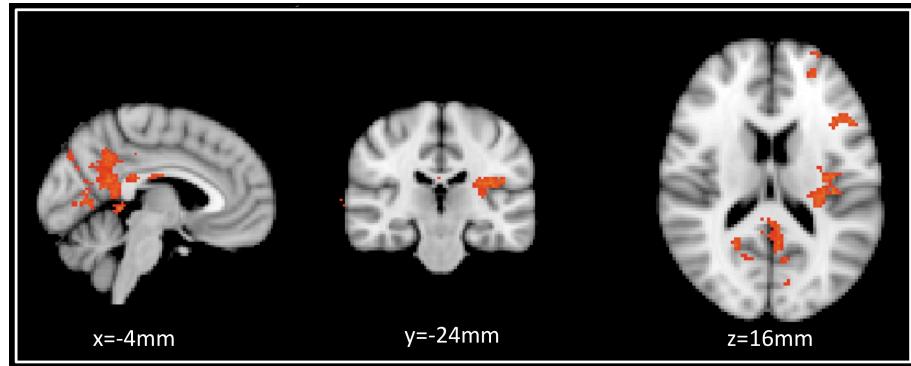
Treatment effect on thermal pain across all three visits. Plot of percentage signal change in the contralateral posterior insular cortex cluster from the Figure 5.13. Mean values for all three visits in the patient group and the baseline and the follow-up visit in the control group.

Fig. 5.16: Treatment effect on heat pain between the baseline and short-term visit



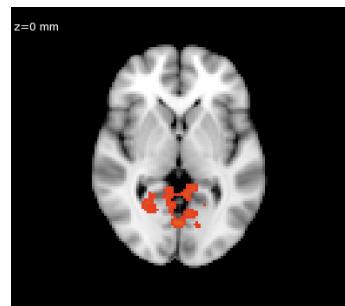
Treatment effect on heat pain between baseline and short-term visit, a two-sample paired t-test, $PAT_{ST} - PAT_{BL}$ contrast. Mixed-effects analysis, $Z > 2.3, p < 0.05$. Differences were observed in the precuneus.

Fig. 5.17: Treatment effect on heat pain between the baseline and long-term visit



Treatment effect on response to heat pain between the baseline and long-term visit. A two-sample paired t-test $PAT_{LT} - PAT_{BL}$ contrast. Mixed-effects analysis, $Z > 2.3, p < 0.05$. Differences were observed in the precuneus, the contralateral insular cortex, and operculum.

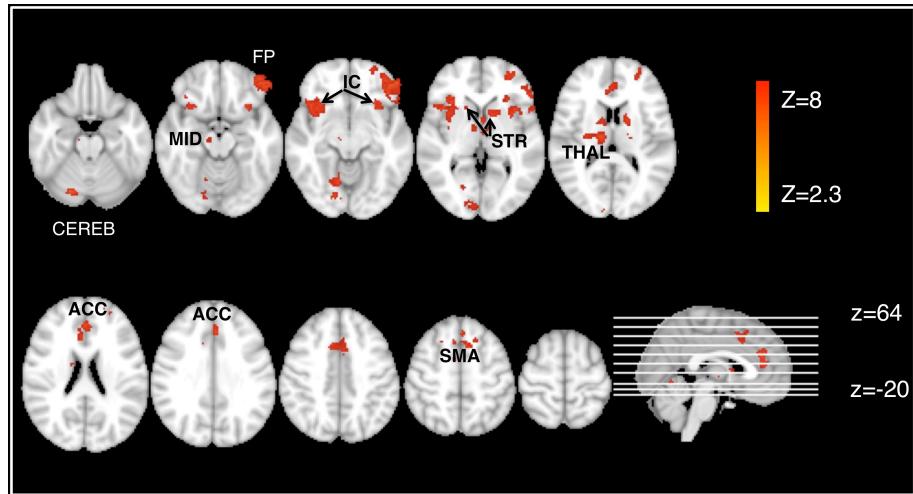
Fig. 5.18: Changes in heat-evoked activation in the patient group controlling for learning effects



Treatment effect on response to heat pain, long-term controlled for learning effect. A two-sample unpaired t-test, $(CON_{BL} > CON_{FU}) > (PAT_{BL} > PAT_{LT})$. Mixed-effects analysis, $Z > 2.3, p < 0.05$. Differences observed bilaterally in the posterior cingulate cortex, the precuneus, and the lingual gyrus.

We have observed a significant reduction in the clinical, psychological and psychophysical variables across all the three visits. The daily pain intensity, tender joint count, disease activity in 28 joints, ESR, and depression scores decreased significantly between the baseline and the short-term visit PAT_{BL-LT} , and were further reduced at the long-term visit PAT_{ST-LT} . This pattern was consistent with the short-term results described in Chapter 4, and suggests that there was an association between changes in inflammation, disease activity, daily pain intensity, and depression scores. These results

Fig. 5.19: Difference in pressure-evoked activation in patients at the long-term visit and matching controls at the baseline



Difference in pressure-evoked activation in patients at the long-term visit PAT_{LT} ($n=11$), and matching controls at the baseline CON_{BL} ($n=11$); a two-sample unpaired t-test. Mixed-effects analysis, $Z > 2.3, p < 0.05$. Differences observed bilaterally in the insular (IC) and anterior cingulate cortices (ACC), the striatum (STR), as well as the ipsilateral thalamus (THAL), the ipsilateral frontal pole (FP) and the cerebellum (CEREB).

were consistent with the clinical studies that demonstrated a decrease of disease activity soon after the start of the anti-TNF treatment and a further decrease within the first six months of the therapy (Hyrich et al., 2006b; Van Vollenhoven et al., 2003; Genta et al., 2006; Kievit et al., 2009; Maini and Feldmann, 2002).

The swollen joint count, duration of joint stiffness, as well as pain ratings for the pressure- and heat-evoked pain decreased significantly over the short-term period PAT_{BL-ST} , and between the baseline and the long-term period PAT_{BL-LT} , but the change between the short- and long-term visit PAT_{ST-LT} was not significant. This is in line with results of the clinical studies, that demonstrated a decrease in inflammatory activity almost immediately after the start of anti-TNF treatment (Elliott et al., 1994), with joint tenderness and stiffness decreasing within days, and joint swelling within the first two weeks (Feldmann, 2002). Both swollen joint count and joint stiffness correspond to the amount of the inflamed joint tissue and effusion (Naredo et al., 2005; Helliwell, 1997), and are the factors that are most likely to affect the nociceptive input during the pressure stimulation used in

this study. This suggests that the reduction of pain ratings for pressure pain might have been related to a decrease in nociceptive input from the stimulated joint. However, there was also a reduction in the duration of morning stiffness which is a symptom associated with general pain in RA (Fields and Martin, 2005). It is also likely that neutralisation of proinflammatory TNF resulted in decrease of inflammation-related pain augmentation. This could explain a decrease in pain ratings for pressure- and for heat-evoked pain. However, pain ratings for pressure pain decreased significantly across all three visits and the ratings at the long-term visit were much lower than at the baseline, whereas the change in heat pain ratings was present only at the short-term visit, and the change between the baseline and the long-term visit was not significant. The reduction in pain ratings at the short-term visit may be related to expectations and reflect a change in report rather than a real reduction in pain (Farrar et al., 2003). The pain report hypothesis would explain why pain rating for heat and for pressure decreased over the short-term. A strong effect over the long-term was present only for the pressure pain, for which the change in pain ratings was more likely to be related to decrease in inflammation, and synovitis. There might have been also a placebo effect, as patients knew that they were taking an active medication; however, it is unlikely, as was discussed in Chapter 4.

The catastrophising scores decreased significantly only between the short-term and long-term visit, unlike the depression scores that showed a decrease at the short-term visit, and further decreased between the short-term and the long-term visit. This would suggest that depression and pain catastrophising do not change together, and that catastrophising is a separate construct from depression (Gracely et al., 2004). In a study by Burns and colleagues (Burns et al., 2003), a decrease in catastrophising occurred early during the cognitive behavioural therapy, and predicted decrease in pain later in treatment. However, in our study the modulated factor was not cognition but pain and inflammation. We observed an early decrease in pain intensity ratings, disease activity and depression scores, but the change in catastrophising scores did not occur until later in the treatment. A large body of literature reported that catastrophising correlates with the intensity of clinical pain, joint tenderness, affective component of pain, as well as disease activity (Edwards et al., 2006; Affleck et al., 1992; Parker et al., 1992b; Keefe et al.,

1989), and that a decrease in catastrophising correlates with a decrease in depression and pain behaviour (Jensen et al., 2001, 1994). The discrepancies may be related to the nature of anti-TNF treatment as it affects pain, mood, and behaviour as has been discussed in Chapter 4. It is plausible that the relationship between pain intensity and catastrophising is not significant and catastrophising could be explained by depression (Affleck et al., 1992; Sullivan and D'Eon, 1990). If that were true, and catastrophising was a cognitive manifestation of depression, the change in catastrophising should have been correlated with the change in depressive scores, but that was not the case. It is important to remember that in our study patients were asked specifically to rate their catastrophising about their clinical pain. It is possible that catastrophising is rather a tendency. Buenaver and colleagues (Buenaver et al., 2008) suggested that catastrophising is a predisposition and it is activated only in the presence of salient, threatening painful stimuli. This would explain why in our study catastrophising only decreased when there was no clinical pain on which to catastrophise.

5.5.1.1 Response and remission

At the long-term visit, all fifteen patients improved and four patients achieved a remission. A remission is defined as a state when there are no or only a few signs of disease (Makinen et al., 2005). It is the ultimate goal of treatment in RA (Combe et al., 2007). The patients who achieved remission were mostly male, with lower than average disease activity score (DAS28), and a lower tender joint count at the baseline. This is in line with the clinical studies as male sex is the major predictor of remission in RA (Forslind et al., 2007; Makinen et al., 2008; Hyrich et al., 2006b), and the DAS28 score at baseline is inversely associated with EULAR remission (Kristensen et al., 2008).

In our study, patients who achieved remission were treated with Adalimumab ($n = 2$), Adalimumab and Methotrexate ($n = 1$), and Etanercept and Methotrexate ($n = 1$). Concomitant Methotrexate is associated with a higher probability of remission (Kristensen et al., 2008), as it enhances the effect of anti-TNF drugs (Maini et al., 1998).

5.5.1.2 Patients after treatment versus controls

We were interested whether the values of the measured variables in the patient group at the long-term visit differed from the values in the control group.

The depression scores in the patient group at the long-term visit did not differ from the scores in the control group at the follow-up visit. This suggests that anti-TNF treatment improves depressive symptoms in RA. It has been reported previously that RA patients treated with anti-TNF have lower frequency of depressive symptoms in comparison to RA patients receiving other treatments (Uguz et al., 2009). It was discussed in the Chapter 4 that anti-TNF treatment may affect mood through changes in cytokine networks (Wichers et al., 2007; Capuron and Miller, 2004), metabolism of neurotransmitters (Zhu et al., 2006; Wichers and Maes, 2002), or hypothalamic-pituitary-adrenal axis (Maes et al., 1993; Reichenberg et al., 2001).

The catastrophising scores in the patient group at the long-term visit were not different from scores in the control group. It was discussed in Chapter 4 that this was probably due to the fact that the clinical pain decreased so there was no pain to catastrophise about (George and Hirsh, 2009; Buenaver et al., 2008).

The pain ratings for heat pain in the patient group did not change significantly at the long-term visit and patients rated heat stimuli as moderately painful². At the long-term visit, patients rated pressure stimuli as more painful than controls, but the ratings were significantly lower than at the baseline. These results would suggest that the psychophysical scores in the patient group normalise after treatment.

5.5.2 Imaging results

5.5.2.1 Treatment effects on pressure-evoked pain

For the pressure-evoked brain activation in the patient group at long-term, there was a significant decrease in activation after anti-TNF treatment. The changes were observed

² not different from 6 out of 10 on the NRS; one-sample t-test $p = 0.065$

in the ipsilateral amygdala and the ipsilateral hippocampus, i.e., the regions that we suggested in Chapter 4 could be used as markers of anti-TNF treatment effects. Changes in these regions were present for the linear trend analysis as well as for the within-subject comparison, i.e., a tripled t-test, for the contrast between the baseline and the long-term visit. There was also a reduction in activation in the contralateral posterior insular cortex, but this effect was less pronounced.

As we discussed in the previous chapter, the amygdala and the hippocampus are important for processing the affective dimension of pain. These structures are also involved in cytokine-induced depressive symptoms, probably via the direct effect of proinflammatory cytokines on these structures as well as through modulation of the hypothalamic-pituitary-adrenal axis. The amygdala is also important for descending pain modulation. Therefore, we suggest that these are the key structures that mediate the effects of TNF inhibition on hyperalgesia, pain behaviour, and mood.

The reduction of activation in the amygdala and the hippocampus might have been related to conditioning or reduction in anxiety. At the follow-up visits patients were no longer scanner-naïve and some of the observed changes could have been related to learning effects, reduction of fear, and boredom.

There was activation in the ventral tegmental area as well as the periaqueductal grey, the nucleus reticularis cuneiformis, and the anterior and mid section of the cingulate cortex. What is important, the activation in the amygdala and hippocampus remained significant even after controlling for conditioning and learning effects. Moreover, a reduction of activation in the patient group in the brainstem, the thalamus, and striatum, became significant only after controlling for possible learning effects. This would suggest that conditioning effects mask changes in pain modulation.

In the brainstem, significant clusters were located in the nucleus reticularis cuneiformis, red nucleus, and the periaqueductal grey. The red nucleus is involved in pain modulation and responds to noxious stimuli mainly from the contralateral side (Bingel et al., 2002; Matsumoto and Walker, 1991; Basbaum and Fields, 1984). The red nucleus receives projections from the periaqueductal grey (Basbaum and Fields, 1984), and modulates thalamic transmission (Steffens et al., 2000). Recently, it has been demonstrated in animal

models that proinflammatory cytokines, such as TNF and IL-1, in the red nucleus are involved in development of allodynia (Wang et al., 2008; Li et al., 2008). The nucleus reticularis cuneiformis is involved in affective, autonomic and effective processing of pain, and responds mainly to salient stimuli such as visceral pain (Dunckley et al., 2005). It has been suggested that the nucleus cuneiformis may be important for chronicity of pain (Williams and Beitz, 1993). It has connections with the periaqueductal grey, rostral ventromedial medulla, and the amygdala. Together with the periaqueductal grey it is involved in central sensitisation in the capsaicin-model and plays an important role in modulation of nociception (Zambreanu et al., 2005). The periaqueductal grey is crucial for the descending control of nociception mainly through the opioidergic system (Basbaum and Fields, 1984). The periaqueductal grey and the red nucleus are involved in aversive conditioning (Sewards and Sewards, 2003; Buchel et al., 1998). It is possible that only after controlling for aversive conditioning we can observe changes in pain modulation in the brainstem.

The thalamus and the striatum are involved in processing the sensory-discriminative as well as the affective-motivational aspect of pain. In our study, changes in the thalamus were present mainly in the medial nuclei involved in the aversive and affective aspects of pain (Albe-Fessard et al., 1985). Other studies have demonstrated that the thalamus is involved in chronic pain (Di Piero et al., 1991; Hsieh et al., 1995; Pagni and Canavero, 1995; Kupers et al., 2000; Derbyshire, 1999; Peyron et al., 2000). The striatum is involved in modulation of nociceptive information (Chudler and Dong, 1995; Bingel et al., 2004).

For the paired comparison between the baseline and the short-term visit, there was a decrease in activation in the contralateral primary somatosensory and motor cortices. This might be related to changes in the stimulus' properties. The primary sensory cortex is involved in processing the discriminatory aspect of stimulus and perceived stimulus intensity (Bushnell et al., 1999; Timmermann et al., 2001). The activation in the primary somatosensory and primary motor cortices is more often evoked by deep pain than by superficial pain (Svensson et al., 1997). This may explain why we observed it for the pressure but not for the heat condition. The primary somatosensory cortex is responsible for the sensory-discriminative aspect of pain. The contralateral primary somatosensory

cortex is activated consistently in the studies where the right upper limb was stimulated, and it is activated more reliably by brief stimuli (Farrell et al., 2005). It is responsible for the sensory-discriminative aspect of pain and the extent of activation is proportional to the perceived pain intensity in experimental and clinical pain (Hofbauer et al., 2001; Porro et al., 2002; Flor et al., 1995; Kanda et al., 2000; Ploner et al., 1999). The primary somatosensory and primary motor cortices are often treated as a functional unit with both sensory and motor functions located in pre- and postcentral gyri (Sobel et al., 1993). In the context of pain, activation in the primary motor cortex most likely reflects inhibition of motor response (Svensson et al., 2003b; Kulkarni et al., 2007). Moreover, a response of the primary motor cortex may be related to muscle bracing during pain (Henderson et al., 2006).

The premotor cortex has been reported to be activated by different types of noxious stimuli (Casey, 1999). This region consists of the supplementary motor area, and the Brodmann area 6. The supplementary motor area is involved in planning and sensory guidance of movements (Mesulam, 2000; Nachev et al., 2008; Arienzo et al., 2006). Activation of the supplementary motor area might also reflect suppression of movement and readiness to withdraw from pain (Apkarian et al., 2005). The premotor cortex Brodmann area 6 is responsible for execution of complex movements and spatial mental operations (Mesulam, 2000). Therefore, reduction of activation in the primary somatosensory, primary motor cortex, premotor cortex, and supplementary area probably reflects the pressure stimuli becoming less painful after treatment.

At the long-term visit, the pressure-evoked pain was only slightly painful but in comparison to activation in the control group it evoked more activation in the regions involved in processing the affective as well as the sensory-discriminative dimension of pain. The changes were mainly present bilaterally in the anterior insular and anterior cingulate cortices, i.e., regions involved in the emotional modulation of pain (Villemure and Bushnell, 2009; Price, 2000; Brooks et al., 2002). In Chapter 4, we discussed that the anterior insular cortex is related to the interoception (Craig, 2003a, 2002). The anterior insula is connected with the anterior cingulate cortex (Augustine, 1996). These regions have been demonstrated to enhance pain behavioural response to injury or inflammation

in persistent pain states (Bolay and Moskowitz, 2002). Therefore, we suggest that after the treatment the pain processing was still altered.

5.5.2.2 Treatment effects on heat-evoked pain

For the heat-evoked pain, brain activation changes were present mainly in the precuneus and the posterior cingulate cortex. As was discussed in the previous chapter, these regions are crucial for self-relevant processing, self-awareness, and integration of sensory information in relevance to self (Northoff et al., 2006; Northoff and Bermpohl, 2004; Cavanna and Trimble, 2006; Price, 2000). Region of interest analysis demonstrated that there was an increase of signal change in these regions across all visits. However, the differences between visits were not significant when a whole-brain paired analysis was performed. These changes were probably small and did not reach significance in the whole-brain analysis. This is consistent with the psychobehavioural results that showed almost non-significant changes in heat-pain ratings between the visits. However, there was a change between the baseline and the long-term visit, as we observed a difference in heat-evoked brain activation between patients and controls at the baseline, which was no longer present at the long-term visit. There was a reduced response in the patient group at the baseline consistent with the study by Jones and Derbyshire (Jones and Derbyshire, 1997), but the activation pattern normalised after an effective treatment. Changes in signal in the precuneus and the posterior cingulate cortex between the baseline and the long-term visit remained significant when corrected for possible learning effect.

We also observed an increase in activation in the contralateral posterior insular cortex. The posterior insular cortex, apart from encoding the sensory-discriminative aspect of pain (Brooks et al., 2002), is involved in the somesthetic-skeletomotor function (Mesulam and Mufson, 1982). An increase of activation, observed in our study, may reflect normalisation of the pain modulation and consequently of the brain activation. The change in the posterior insular cortex suggest an increase in pain transmission as the input remained constant. As discussed in Chapter 3, there was less activation in the posterior insular cor-

tex in the patient group than in controls at the baseline visit, which would confirm that there is normalisation of pain processing after the treatment.

In the Chapter 4, we discussed that the precuneus and the posterior cingulate cortex are important for attention and integration of sensory information in relevance to self. These regions belong also to the default mode network, also called task-negative network, because activation in these regions decreases during complex tasks. In this chapter, there was a consistent change in activation in these regions, present already at the short-term visit. We propose that the observed activation pattern reflects changes in attention, self-awareness, and self-referential processing related to reduction of the ongoing clinical pain. Probably, in the presence of ongoing clinical pain, the response to experimental pain is reduced, as all the cognitive resources are concentrated on clinical pain. It is plausible that the deactivation observed at baseline corresponds to the medial prefrontal cortex being "shut down" during experimental pain as was suggested by Vogt (Vogt, 2005). Perhaps, in the presence of strong chronic pain the neurophysiological resources are already engaged and the emotional valence of additional painful stimulus is not processed, especially when it is a less threatening, experimental stimulus. This might be the reason why these changes were present for heat but not for pressure stimulation. As the clinical pain decreases after treatment, patients attend more to the experimental pain and begin to process it as self-relevant. This would, at least partly, explain an increase of heat-evoked brain activation after the treatment.

5.6 Main findings

- The clinical and psychological measured variables decreased significantly across the visits; the effect was least pronounced for the heat pain ratings.
- The disease activity score and ESR decreased significantly across the visits, along with the reduction in the intensity of daily pain, tender joint count and depression scores. The pain ratings for pressure and heat pain, swollen joint count, and duration of joint stiffness decreased significantly only between the baseline and the short-term visit,

whereas the catastrophising scores decreased significantly only between the short-term and the long-term visit.

- After the treatment, heat pain ratings, depression, and catastrophising scores in the patient group were not significantly different from the values in the control group; the ratings for pressure pain were higher than in the control group but lower than before the treatment.
- For the pressure condition, there was a decrease in activation in the ipsilateral amygdala and the hippocampus, i.e., the regions suggested to reflect the effects of anti-TNF treatment in Chapter 4. After the effective treatment, there was a reduction of activation in response to pressure in the patient group, and the activation was observed mainly in the regions processing affective dimension of pain and interoception.
- For the heat condition, there was an increase of signal change mainly in the precuneus and the posterior cingulate cortex. These changes most likely reflect modulation of the attentional load and self-referential processing related to improvement in general health and reduction of ongoing, clinical pain. In the patient group, the brain response evoked by heat pain normalised after successful treatment.

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