

Pain in rotator cuff tendinopathy and its changes after arthroscopic decompression, placebo surgery, and conservative management – a QST and neuroimaging study

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ABSTRACT

Background

Pain in tendinopathy, including shoulder impingement syndrome, is thought to be driven by pathology in the periphery as well as changes in the sensory processing within the central nervous system.

Methods

This is a neuroimaging extension of the “Can Shoulder Arthroscopy Work? (CSAW) trial investigating efficacy of arthroscopic shoulder decompression (ASAD) in comparison to arthroscopy only (AO) and a non-interventional control group (AMSR) in patients with chronic shoulder pain due to impingement. The aim of this study was to investigate responses to mechanical stimuli and their change at 6-months follow-up in each of the trial arm.

Results

67 patients at 24 healthy controls were assessed at baseline and 54 patients returned for a follow-up visit. QST demonstrated presence of hypoesthesia and deep pain allodynia in the patient group. In neuroimaging results, hypoesthesia was reflected by reduced stimulus-evoked activation in somatosensory regions in the patient group. At the follow-up, the QST profiles did not change in any of the trial arms. Brain activation increased in the midcingulate/paracingulate gyrus across all trial arms, and there was significant difference in post-treatment changes between the placebo and the surgical arm. Ratings for stimulus sharpness correlated with activation in the frontal regions in the placebo arm and in the hippocampus in the non-interventional arm, reflecting placebo and nocebo response, respectively.

Conclusions

Neither QST nor brain imaging results provide evidence that surgery results in more preferable results than surgical placebo or non-interventional treatment. Neuroimaging is potentially useful to explain mechanisms that drive patient-reported outcomes in clinical trials.

Key words: quantitative sensory testing, QST, chronic pain, musculoskeletal pain, central sensitisation, neuropathic pain, PainDETECT

CSAW – 29th September 2017

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INTRODUCTION

Shoulder pain is highly prevalent [73][26][47] and often leads to persistent problems as less than half of patients report full recovery after 18 months.[14][74] The most

common cause of shoulder pain is rotator cuff tendinopathy, which is thought to result from a mechanical conflict between the acromion and tendons.[73] A popular treatment involves surgical removal of part of the acromion to create more space for the tendons (decompression); although, this surgery does not always lead to better results than conservative management[19][9]. It is likely that the mechanical conflict between the bone and the tendons is not the only cause of pain in this condition; other suggested pain mechanisms include inflammation[18] or changes within the central nervous system [71] and central sensitisation [27] [53].

Central sensitisation, i.e., increased responses of central nervous system neurones to an input from the periphery, is likely to be responsible for at least some of the signs and symptoms present in shoulder pain patients, including reduced pain threshold (allodynia) and increased pain responses to painful stimuli (hyperalgesia).[12][28][60] Pain phenotyping[49] and assessment of pain sensitisation[4][63] can be performed using Quantitative Sensory Testing (QST), which unlike unidimensional pain ratings scales, provides an insight into mechanisms underlying sensory changes and pain.[49,58] Earlier studies demonstrated that patients with shoulder impingement have an increased pain response to pain stimuli (Mechanical Pain Threshold) [28] and lower Pressure Pain Threshold (PPT).[52] PPT on affected side was shown to correlate with shoulder pain.[12] Bilateral increase in Mechanical Detection Threshold (MDT) have been reported in patellofemoral pain syndrome [35],[34]. Apart from signs of sensitisation, about 30-40% patients with musculoskeletal pain have a neuropathic component to their pain.[36]

There have been no neuroimaging studies on tendinopathies, neither on altered responses to sensory stimuli nor on clinical ongoing pain. Experimental studies on secondary mechanical hyperalgesia demonstrated that central sensitisation is maintained by activation changes in the brainstem, mainly the periaqueductal grey matter, nucleus cuneiformis, and rostral ventromedial medulla.[76] [43]

AIMS

The aim of this study was to investigate changes in stimulus-evoked brain activation (primary outcome) as well as in pain ratings, and the QST profile after surgery, i.e., arthroscopic subacromial decompression (ASAD) and compare them to changes after a quasi-placebo intervention, i.e., arthroscopy only (AO) and a natural history of disease (non-interventional arm, Active Monitoring with Specialist Reassessment, AMSR) in order to explain the mechanisms responsible for reported improvement after treatment.

As the knowledge about pain mechanisms in shoulder pain is relatively limited[60] this study also offered an opportunity to characterise pain in rotator cuff tendinopathy using QST as well as to analyse the relationship between reported pain, QST, and brain activation.

We hypothesised that: 1) at the follow-up, the activation would change in the ASAD group in comparison with the AMSR and AO group and that the changes would reflect reduction of nociceptive input and central sensitisation, whereas in the AO arm there

1 will be changes in activation related to placebo effect, 2) the sensory phenotype
2 between patients and controls, as assessed using QST, would be different and that
3 differences would be present not only on the affected side but also over the
4 contralateral shoulder suggesting central sensitisation, 3) the QST values would
5 explain the pain ratings and stimulus-related brain activation, and would predict OSS
6 after intervention.

10 METHODS

11 Trial outline

12 This study was an extension of a multicentre randomised controlled trial “Can
13 Shoulder Arthroscopy Work?” (CSAW), which investigated the efficacy of arthroscopic
14 subacromial decompression (ASAD) for rotator cuff tendinopathy by comparing it to
15 effects of a quasi-placebo in a form of diagnostic arthroscopy (AO: Arthroscopy only)
16 and to a conservative treatment (AMSR: Active monitoring with specialist
17 reassessment)). The study rationale and design, including details of allocation,
18 randomisation and blinding, have been described previously.[5] In brief, ASAD is a
19 minimally-invasive intervention, which consists of removal of a bony spur on the
20 acromion to create more space for rotator cuff tendons. This is a very common
21 procedure but there are doubts whether it is really effective.[9][19]

22 Participants

23 Patients were recruited from outpatient clinics at the Nuffield Orthopaedic Centre,
24 Oxford, UK (one of the centres participating in the CSAW trial), whereas healthy
25 controls volunteered in response to advertisements.

26 The inclusion criterion was presence of subacromial pain due to tendinopathy or
27 partial tear, which lasted at least three months despite conservative treatment.
28 Patient's diagnosis was confirmed by a consultant surgeon. The exclusion criteria
29 were: age over 75 years, diagnosis of a full-thickness tear or calcific tendonitis,
30 previous surgical treatment on the affected shoulder, inflammatory disorder of the
31 joints, or symptomatic cervical spine pathology. Participants with a history of
32 psychiatric or neurological condition that might have affected pain ratings or with
33 contraindications for magnetic resonance imaging (MRI) were also excluded. Control
34 participants were included if they were pain-free, younger than 75 years, in general
35 good health, and without contraindications for MRI.

36 The study was performed according to the Declaration of Helsinki and approved by
37 the National Research Ethics Service (NRES) South Central–Oxford B Research
38 Ethics Committee (Reference number: 12/SC/0028). All participants signed an
39 informed consent at the beginning of the first visit.

40 Procedures

41 Eligible participants attended a baseline assessment visit, during which they
42 underwent the mechanical part of the QST, completed a standardised researcher-

1 administered pain appraisal form, and questionnaires assessing shoulder pain and
2 function (Oxford Shoulder Score, OSS), presence of neuropathic pain component
3 (PainDETECT, PD-Q) as well as anxiety and depression (Hospital Anxiety and
4 Depression Scale, HADS). Patients also rated their expectations regarding treatment
5 outcome on a 7-point Likert scale from “-3 – very much worse” to “+3 – very much
6 improved”; the same scale was used to rate Patient Global Impression of
7 Change(PGIC) at the follow-up visit. All participants were asked not to take any
8 analgesic medication 24 hours before the scanning session.
9

10
11 **Pain assessments and questionnaires**

12 The primary outcome in the main trial was Oxford Shoulder Score (OSS), which is a
13 self-reporting questionnaire assessing the severity of shoulder-related pain and
14 function. The possible range is from 48 being the best score to 0 being the worst.[17]
15

16 Present pain intensity (PPI) was measured on a 11-point numerical rating scale
17 (NRS), from 0 - “no pain” to 10 - “worst pain possible”. Pain duration, radiating pain,
18 abnormal sensations (paraesthesia, dysesthesia), comorbidities and medication were
19 also recorded during the clinical assessment at the beginning of the visit.
20

21 Patients also completed the PainDETECT questionnaire (PD-Q), which had been
22 developed as a screening questionnaire for neuropathic component in lower back
23 pain[22] but has since been used to assess other types of chronic pain.[51]. Possible
24 scores range from 0 to 38 and values below or equal 12 suggest that pain is probably
25 nociceptive and that the neuropathic component is unlikely, whereas values equal or
26 larger than 19 suggest that a neuropathic component is likely; scores between 12 and
27 19 mean that the result is uncertain.[22] However, diagnosis of neuropathic pain
28 using questionnaires is not straightforward and does not identify all the patients with
29 neuropathic pain component.[15,29]

30 As anxiety and depression are known to mediate the relationship between pain and
31 disability;[42][13][50] they were assessed using the Hospital Anxiety and Depression
32 Scale (HADS). The higher the score the worse the result, with the maximum score
33 being 21 for each factor and a score over 10 being considered definitely
34 abnormal.[77]
35

36
37 **QST**

38 QST was performed according to the protocol developed by the German Research
39 Network on Neuropathic Pain (DFNS).[58][59] Assessment was done by a single
40 researcher (KAW) who had undergone training with the DFNS group in Kiel,
41 Germany.
42

43 Three different mechanical sensitivity thresholds were measured: mechanical
44 detection threshold (MDT), mechanical pain threshold (MPT), and pressure pain
45 threshold (PPT) because studies suggested that these modalities may be affected in
46 tendinopathies. [35][52][28] The tests were performed over the deltoid tuberosity of
47 humerus of the affected as well as on the contralateral shoulder.
48

Mechanical sensitivity for tactile stimuli, i.e., Mechanical Detection Threshold (MDT), was assessed using a set of 20 standardised von Frey monofilaments (Touch Test, Stoetling, USA). Five series of descending and ascending stimuli were applied for one second and participants were asked to report whether they perceived the stimulus.

Mechanical Pain Threshold (MPT) was determined using a set of seven weighted stimulators with flat contact area, 0.25mm in diameter, with calibrated pressure devices ranging from 8 to 512mN (MRC Systems, Germany). Five ascending and descending series of stimuli were applied for about one second and subjects were asked whether they perceived the stimulus as blunt or sharp.

Pressure Pain Threshold (PPT) was assessed using a hand-held pressure gauge device with a 1cm² rubber probe (FDN100, Wagner Instruments, USA). PPT was measured three times by slowly increasing the pressure at a rate 5N/s until the participant reported that the sensation of pressure turned into a sensation of pain.

The order of QST tests was the same for all participants but the side order affected/contralateral (or left/right in the control group) was randomised using a computer-generated sequence. The averaged result was calculated using the geometric mean for MDT and MPT and the arithmetic mean for PPT.

Imaging Protocol

The same stimulus was used for all participants. During an imaging session, 15 punctate stimuli were delivered to the area over deltoid tuberosity of humerus of the affected shoulder. A 26g von Frey monofilament was applied for one second. The inter-stimulus interval was randomly jittered between 29 and 33 seconds to prevent expectations and habituation.[76] At the end of the scan patients were asked to verbally rate the intensity of pain and sharpness related to the stimulus as well as the intensity of ongoing shoulder pain during the scan on the 11-point numerical rating scale. We collected the average pain ratings rather than ratings of individual stimuli because individual ratings interfere with stimulation-related BOLD, lead to longer inter-stimulus intervals, and subsequently, to longer experiment. [76]

Neuroimaging data was acquired on a 3T Verio MRI scanner (Siemens, Erlangen, Germany) using a 32-channel head coil.

BOLD imaging scans were acquired with a standard gradient EPI sequence using the following parameters: repetition time (TR) 2410ms, echo time (TE) 30ms, acceleration factor GRAPPA 2, flip angle 90 degrees, FOV 192x192mm, and 64x64 matrix. There were 199 volumes; each image had 44 slices with 3x3mm in-plane resolution, and 3mm slice thickness.

Field map images were collected using a gradient echo sequence with repetition time (TR) 438ms, echo times (TE1) 5.19ms and (TE2) 7.65ms, flip angle 60 degrees and the same FOV and resolution as the functional BOLD.

A T1-weighted high-resolution structural scan was acquired for the purpose of registration and anatomical overlay of activation. The parameters were as follows: TR 2040ms, TE 4.7ms, inversion time 900ms, flip angle 8 degrees, FOV 192x174mm,

1mm isometric voxels.

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2 Outcomes
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4 The primary outcome was the effect of ASAD in comparison to AO and AMSR on
5 QST measures, and stimulus-evoked brain activation.
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8 We also investigated the association between brain activation and pain-related
9 outcomes, QST measures (controlling for psychological and demographic variables at
10 baseline), and the relationship between changes in pain ratings and brain activation
11 after the treatment. In addition to that, we also analysed whether the QST values and
12 expectations at baseline predict of post-treatment improvement (defined as OSS at
13 the follow-up).
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16 Demographic, clinical, and psychobehavioural data analysis
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18 *Descriptive statistics*
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20 Continuous, normally-distributed variables were reported as means and standard
21 deviations (SD), not normally-distributed variables as medians and interquartile range
22 (IQR), and categorical variables as frequencies.
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24
25 An ANOVA and Fisher's exact test were used to investigate whether there were any
26 differences between trial arms at baseline, because; although, in the main trial,
27 patients were randomised into three arms with minimisation for age, sex, and
28 baseline OSS, only a subset of patients participated in the neuroimaging study.
29
30

31 *QST characteristics*
32
33 Central sensitisation was defined as hypersensitivity or hyperalgesia to mechanical
34 stimuli on the unaffected, contralateral side.[21][44][60] Changes on the affected side
35 were interpreted as results of primary and secondary hyperalgesia.[16][38]
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38 Mean QST values were log-transformed as QST measures tend to be right
39 skewed.[59]
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42 A paired t-test was used to investigate the differences in QST scores between the
43 affected and non-affected shoulder in the patient group, whereas an ANOVA was
44 used to investigate differences between the QST values in the patient and the control
45 group, controlling for age and sex, because QST scores depend on age and
46 sex.[7][41][58][48]
47
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49 The log-transformed QST values were also converted into Z-scores for visualisation
50 purposes and to facilitate comparison with the literature; therefore, they were used to
51 present QST values and baseline and the follow-up and the paired differences.
52 Normative data used for Z-score transformation are presented in the Appendix (**Error!**
53 **Reference source not found.** and **Error! Reference source not found.**). Log-
54 transformed QST measures, with age and sex as covariates, were used in the
55 between-group and between-arm analyses.
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59 *Interactions between pain outcomes, QST, and clinical variables at baseline*
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61 Associations between pain report at baseline and QST variables were analysed using
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stepwise regression with backward and forward selection. We have investigated the pain outcomes, OSS, PPI, and von Frey ratings, controlling for demographic, clinical, psychological. The model included the following explanatory variables: logMDT, logMPT, logPPT (on the affected and contralateral side, separately), age, sex, HADS, PD-Q, presence of other pain condition, disease duration (log-transformed so that it was normally distributed), presence of radiating pain, presence of abnormal pain sensations, high expectations and very high expectations. For von Frey ratings the model also included ratings for ongoing pain during the scan. We have also used logistic regression to investigate whether QST values explain reported paraesthesiae/dysesthesiae and radiating pain

Effect of treatment

Treatment effect on pain-related outcomes and QST measures was analysed using a linear regression of follow-up values adjusting for baseline values, age, and sex. We also used post-hoc paired t-tests to investigate the differences within each trial arm.

Predictive value of QST and expectations

Predictive value of QST variables (controlled for demographic, clinical and psychological variables) was analysed using stepwise regression with backward and forward selection.

All statistical analysis was preformed using STATA software version 13.1 with $p<0.05$ considered statistically significant. Stepwise regression analysis with forward and backward selection was performed using R version 3.3.3 with the best model chosen using the Akaike Information Criterion (AIC) method and confidence intervals (CIs) calculated using the Wald method.

FMRI data analysis

FMRI data were analysed using the FSL (FSL, www.fmrib.ox.ac.uk/fsl) package. The pre-processing steps involved motion correction using MCFLIRT[32], B_0 unwarping, and spatial smoothing with a Gaussian kernel of 5mm FWHM. Motion artefacts were removed using ICA-AROMA [55] and cleaned data were filtered using a high-pass filter cut-off of 90 seconds.

The first level statistical analysis consisted of a general linear modelling using a generalised gamma variate hemodynamic response function (HRF) representing the BOLD signal evoked by sensory stimulation. A single contrast was used representing the punctate stimulation versus baseline. A mean average image was created using FLAME1. Statistical parametric maps were thresholded at a $Z=3.1$ with a cluster significance of 0.05.

For group analysis, data were registered to a study-specific template using an affine (FLIRT)[33] and then nonlinear (FNIRT)[2] transformation. For patients with affected left shoulder and for controls with stimulation on the left shoulder data were flipped along the x-axis so that the activation was consistently ipsi- or contralateral to the affected arm.

The study-specific template was created by averaging structural scans of an even number of patients and controls, affine transforming them to the standard MNI152_T1 template, creating a mean, and an x-axis flipped mean image then averaging it to create a new template. Then the individual structural scans were registered to the template using an affine and non-linear transformation, averaged, flipped along x-axis and averaged again to create a study-specific symmetrical template.

Local maxima coordinates were transferred from symmetrical study-specific template to MNI space.

Associations between brain activation and psychophysical and clinical variables at baseline

We used a one-sample t-test with covariates to investigate whether stimulus-evoked brain activation was explained by altered sensory processing reflected by logMDT scores on the affected side, sharpness ratings for the sensory stimulus, ongoing pain ratings, HADS scores, age, and sex.

Differences between the patient and control group

Two-group unpaired t-test with age and sex as covariates of no interest was used to compare stimulus-evoked brain activation between patients and controls.

Treatment effect

The effect of treatment was analysed using a 2-level repeated measures analysis within- (design 1) and between-arms (design 2) models (Appendix – Treatment effect analysis models).

Post-hoc analysis of within-arm effect

Treatment effect within each arm was investigated using a paired t-test. In order to explain what drives reported pain ratings for von Frey stimulus intensity and ongoing pain were also entered into the paired t-test model.

Sensitivity analysis

The effect of treatment was also analysed using a three-level analysis: the first-level individual patient results were used, at the second level, in a fixed-effect analysis to create a baseline versus follow-up difference for each patient. At the third level, we compared the differences between the arms and an F-test across the arms (Appendix – Treatment effect analysis models).

Power analysis

Power calculations were based on BOLD FMRI data from previous neuroimaging studies on mechanical stimulus-evoked pain in patients with rheumatoid arthritis and patients with shoulder pain. It was estimated that at least 25 subject per group were needed to detect a difference in treatment effect between groups with alpha=0.05 and 80% power.

The study was designed back in 2012; therefore, power was calculated for Z=2.3. Data collection finished before the paper by Eklund et al.[20] was published, and although the sample size could not have been increased, the results were reported for Z=3.1.

RESULTS

Participants' characteristics

Eighty-four patients were recruited by the Oxford centre into the CSAW trial. From this group, 67 patients participated in the neuroimaging extension of the trial. Moreover, 24 pain-free controls were recruited into the neuroimaging study. Follow-up data were available for 54 patients (81%). Two patients withdrew from the trial and 11 were lost to follow-up. There was no follow-up visit for healthy controls. CONSORT Flow Chart is presented in Figure 1.

Patients and controls were matched with respect to age and sex: patients' mean age was 51.4 ± 11.5 and controls' mean age was 48.8 ± 8.1 ($t=-1.0$, $p=0.3$); 37% of subjects in each group were female.

Patients randomised to different study arms were comparable with respect of demographic and clinical variables (Figure 1 and Table 1). Most of the patients had affected right shoulder (69%). The median disease duration was 24 months (IQR 18–36). The mean OSS was 27.3 (SD 7.7) and mean HADS was 11.7 (SD 7.5). Mean Present Pain Intensity (PPI) reported at rest during the assessment visit was 2.9 (SD 2.4).

Two thirds of the patients (66%) had PD-Q scores equal or below 12, suggesting nociceptive pain mechanisms, and 19% had scores equal or above 19 suggesting neuropathic pain component (Figure 2). 81% ($n=54/67$) of patients reported radiating pain and 48% ($n=32/67$) reported abnormal pain sensation such as paraesthesiae and dysesthesiae.

As 87% of patients rated von Frey stimulation as not painful, sharpness ratings were used for correlations with neuroimaging BOLD data. The mean sharpness rating for the von Frey stimulus was 2.5 (SD 2.5) of 10 and the mean ongoing pain during the BOLD FMRI scan was 2.3 (SD 2.6).

Expectations

Patients had generally positive expectations regarding their pain and function after the trial (a score between +1 and +3 on the Likert scale) (Table 1). All of them reported that they expect improvement, with 26% expecting their pain and function to "much improve" and 38% expected it to "very much improve". There was only one patient in the AO group who expected no difference and as this was the only value in this category, "0" was merged with the "+1" for all the analyses. As patients gave only three answers out of possible seven, we investigated the effect of high and very high expectations in comparison to moderate expectations, i.e., we compared the "+2

much improved group" to "*+1 minimally improved*" and "*+3 very much improved*" to "*+1 minimally improved*".

When asked at the follow-up visit about their impression of change (PGIC) patients in all trial arms reported improvement and there was no significant difference between the arms: Kruskal-Wallis chi-squared (with ties) =2.22, 2 d.f. p=0.33; ASAD median=2 (IQR=3), AO median=1 (IQR=1), AMSR median=1 (IQR=2).

High and very high expectations ("*+2 much improved*" and "*+3 very much improved*" versus "*+1 minimally improved*") were associated with lower pain intensity (PPI) at the follow-up: $\beta=-1.5$ (95%CI -2.88, -0.13, p=0.033) for high expectations and $\beta=-1.81$ (95%CI -3.16, -0.45, p=0.010) for very high expectations, corrected by age, sex, baseline pain scores, and trial arm.

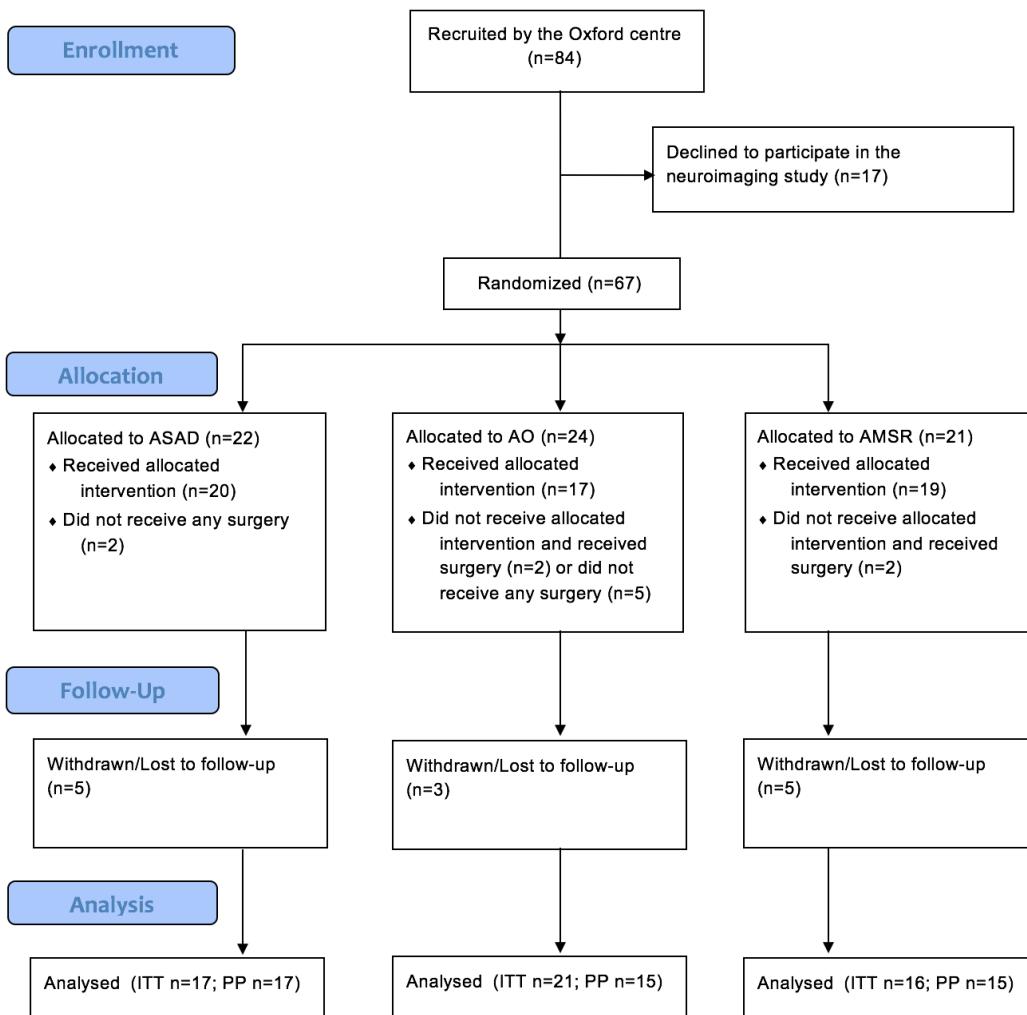


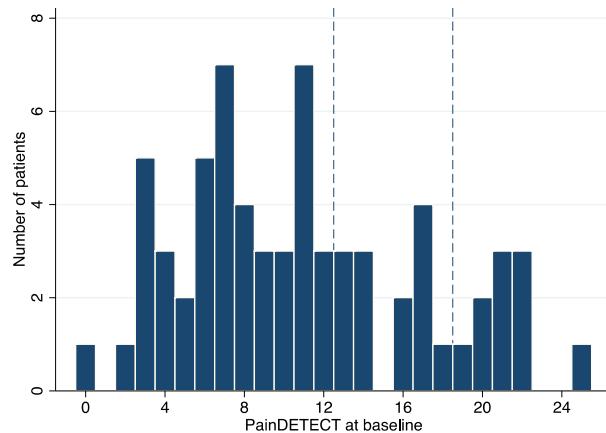
Figure 1 – CONSORT Flow Chart

Table 1 – Demographics and clinical characteristics

Baseline characteristics	All patients N=67	ASAD N=22	AO N=24	AMSR N=21	Between-groups comparison (ANOVA/ Fisher's exact test)
Age in years, Mean \pm SD	51.4 \pm 11.5	51.5 \pm 10.4	52.4 \pm 12.8	50.1 \pm 11.4	F(df2) = 0.22, p=0.81
Female, N (%)	25 (37%)	7 (32%)	12 (50%)	6 (29%)	chi2(df2) = 59.81, p=0.5
Right shoulder affected, N (%)	46 (69%)	13 (59%)	16 (67%)	17 (81%)	chi2(df2) = 2.5, p=0.31
Symptoms duration in months, Median (IQR*)	24 (18-36)	24 (18-36)	24 (18-36)	26 (14-48)	F(df2) = 0.24, p=0.89 &
Oxford Shoulder Score (OSS), Mean \pm SD	27.3 \pm 7.5	26.0 \pm 6.8	29.1 \pm 7.7	26.7 \pm 8.0	F(df2) = 1.08, p=0.35
Present Pain Intensity (PPI), Mean \pm SD	2.9 \pm 2.4	2.4 \pm 2.2	3.6 \pm 2.5	2.7 \pm 2.4	F(df2) = 1.8, p=0.17
PainDETECT (PD-Q), Mean \pm SD	10.9 \pm 6.0	12.2 \pm 6.3	10.1 \pm 6.0	10.5 \pm 5.9	F(df2) = 0.79, p=0.46
PD-Q \leq 12 , N (%)	44 (66%)	11/22 (50%)	19/24 (79%)	14/21 (67%)	chi2(df2) = 4.34, p=0.12
PD-Q 12- 19, N (%)	10 (15%)	7/22 (32%)	1/24 (4%)	4/21 (19%)	chi2(df2) = 4.10, p=0.14
PD-Q \geq 19 , N (%)	13 (19%)	4/22 (18%)	3/24 (13%)	3/21 (14%)	chi2(df2) = 0.30, p=0.91
HADS total score, Mean \pm SD	11.7 \pm 7.5	12.6 \pm 7.4	11.1 \pm 6.7	11.4 \pm 8.6	F(df2) = 0.25, p=0.78
Anxiety subscale, Mean \pm SD	6.7 \pm 4.4	7.1 \pm 4.2	6.7 \pm 4.3	6.3 \pm 4.7	F(df2) = 0.26, p=0.88
Depression subscale, Mean \pm SD	5.0 \pm 4.0	4.4 \pm 3.1	5.5 \pm 4.0	5.5 \pm 4.0	F(df2) = 0.46, p=0.63
Expectations:					chi2(df2) = 4.93, p=0.57
very much improved	25 (38%)	6 (27%)	12 (50%)	7 (33%)	
much improved	17 (26%)	7 (32%)	4 (17%)	6 (29%)	
minimally improved	23 (35%)	8 (36%)	7 (29%)	8 (38%)	
no change	1 (2%)	0 (0%)	1 (4%)	0 (0%)	
von Frey sharpness, Mean \pm SD	2.5 \pm 2.5	2.4 \pm 2.5	2.0 \pm 2.4	3.5 \pm 2.4	F(df=2)=2.27, p=0.11
von Frey pain, Mean \pm SD	0.5 \pm 1.5	0.98 \pm 2.2	0.38 \pm 1.1	0.06 \pm 0.2	F(df=2)=1.99, p=0.15
von Frey ongoing, Mean \pm SD	2.3 \pm 2.6	2.1 \pm 2.3	2.2 \pm 2.4	2.6 \pm 3.2	F(df=2)=0.22, p=0.80
Pain-killers on the day, N (%)	20 (30%)	6/22 (27%)	7/24 (29%)	7/21 (33%)	chi2(df2) = 0.20, p=0.95
Radiating pain, N (%)	54 (81%)	17/22 (77%)	19/24 (79%)	18/21 (86%)	chi2(df2) = 0.54, p=0.80
Abnormal sensation, N (%)	32 (48%)	11/22 (50%)	8/24 (33%)	13/21 (62%)	chi2(df2) = 3.73, p=0.16
Other pain, N (%)	30 (45%)	15/22 (68%)	12/24 (50%)	11/21 (52%)	chi2(df2) = 1.78, p=0.44

* - Interquartile Range

& - Kruskal-Wallis (non-parametric equivalent of ANOVA)

**Figure 2 - PainDETECT scores at baseline**

Vertical lines mark the 12 and 19 cut-off values

QST

In the patient group there were differences between the affected and non-affected arm only for PPT. The logPPT was lower on the affected side ($t=-2.34$, $p=0.02$) but there was no significant difference between the affected shoulder and the sternum ($t=-0.24$, $p=0.81$) or between the contralateral shoulder and the sternum ($t=1.94$, $p=0.057$). There were no significant pair-wise differences between the affected and contralateral side for logMPT ($t=1.3$ $p=0.21$) or logMDT ($t=-0.72$ $p=0.64$).

There were no differences between sides in the control group for any of the QST measures (logPPT $t=-0.65$, $p=0.52$; logMDT $t=0.29$, $p=0.77$; logMPT $t=0.24$, $p=0.81$).

The order of assessment, i.e., which side was assessed first, did not significantly affect the log-transformed QST values.

When patients' log-transformed QST values were compared to controls' data, controlling for age and sex, patients' logMDT values were higher on the affected ($Z=7.2$, $p=0.009$) and contralateral side ($Z=8.4$, $p=0.005$) and the logPPT values were lower on the affected ($Z=14.0$, $p=0.0004$) and contralateral side ($Z=10.3$, $p=0.002$) as well as on the sternum ($Z=18.22$, $p=0.0001$). There were no differences between patients and controls for logMPT.

QST were also Z-transformed. Reversed Z-scores (rZscores) were used so that lower values reflected loss of function and higher values reflected gain of function (Figure 3). Hypoesthesia (low rZscores for MDT) was present on the affected side in 27% of patients and on the contralateral side in 25% of patients. Allodynia to deep pressure (high rZscores for PPT) was present on the affected side in 23% of patients, on the contralateral side in 18% of patients, and on the sternum in 28% of patients (**Error! Reference source not found.** and **Error! Reference source not found.**).

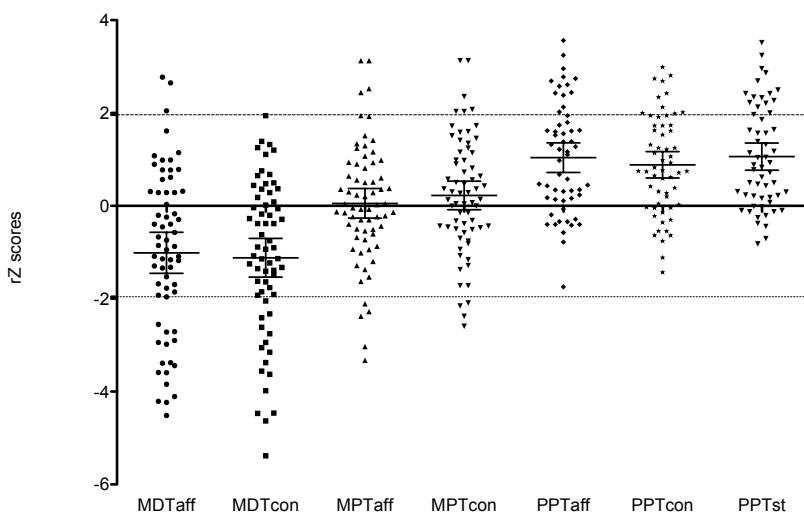


Figure 3 – Reversed QST Z-scores

The bar marks the mean and 95%CI. rZ scores – reversed Z score; MDT – Mechanical Detection Threshold; MPT – Mechanical Pain Threshold; PPT – Pressure Pain Threshold; aff – affected side, con – contralateral side; st - sternum

Interactions between pain outcomes, QST and clinical variables at baseline

We also investigated whether QST values explain reported pain.

In the univariate analysis, worse OSS scores were associated with hypoesthesia (higher logMDT) on both sides, allodynia to deep pressure (lower logPPT) on the affected side, higher HADS, higher PD-Q, and high expectations vs low expectations (**Error! Reference source not found.**). In a multivariate analysis, worse OSS scores were associated with hypoesthesia and allodynia to deep pressure on the affected side, higher PD-Q scores, and high expectation (**Error! Reference source not found.**).

The only variable associated with higher PPI at baseline in a univariate analysis was PD-Q (**Error! Reference source not found.**) and no variables were significant in the multivariate analysis (**Error! Reference source not found.**).

Sharpness of von Frey stimulation reported after the scan was associated with higher ongoing pain during the scan, less hypoesthesia (lower logMPT) on the affected side, younger age, and female sex, in a univariate analysis (**Error! Reference source not found.**). In a multivariate analysis, higher ratings for sharpness were associated with higher ongoing pain, and younger age (**Error! Reference source not found.**).

There was a strong relationship between reported abnormal sensation (i.e., paraesthesiae, dysesthesiae) and radiating pain (Fisher's exact test =10.4 p=0.001). Both of these symptoms were associated with pressure pain hyperalgesia (lower logPPT) on the contralateral side at baseline (radiating pain: t=-2.05, p=0.045 and abnormal sensations: t=-2.18 p= 0.034).

Treatment effect

Outcome measures at the follow-up and within-arm effect in the intention-to-treat analysis are presented in Table 2 and the between-arm effect in Table 3. There was a significant improvement in OSS in all arms arm but no difference in the effect between the arms. Pain intensity at rest during a visit (PPI) decreased in the placebo arm (with a trend in the surgical arm) and there was a significant between-arms effect. However, the ongoing pain during the scan decreased only in the surgical arm and there was no between-arm difference. PD-Q score was reduced at follow-up in the surgical and the placebo arm but not in the non-interventional arm and there was also no significant between-arm effect. There were no significant within- or between-arm changes in any of the QST measures. (Please note that the p values were not corrected for multiple comparisons.)

Table 2 – Within-arm changes in clinical and psychological measures

<i>Intention-to-treat</i>	<i>Baseline</i>	<i>Baseline</i>	<i>Follow-up</i>	<i>Difference</i>	<i>Paired t-test p</i>
<i>ASAD</i>	<i>(pair)</i>				
OSS	26.0 ± 6.8 (N=22)	27.0 ± 6.7	35.6 ± 9.7	8.6 ± 10.4 (N=18)	0.003
PPI	2.4 ± 2.3 (N=22)	2.3 ± 2.1	1.1 ± 2.0	-1.2 ± 2.6 (N=18)	0.07
PD-Q	12.2 ± 6.3 (N=22)	11.3 ± 5.9	7.9 ± 5.6	-3.4 ± 5.3 (N=18)	0.02
HADS	12.6 ± 7.4 (N=22)	11.8 ± 7.6	8.7 ± 10.5	-3.2 ± 6.9 (N=18)	0.07
MDT affected	-1.3 ± 1.7 (N=20)	-0.9 ± 1.6	-0.8 ± 1.7	0.04 ± 1.7 (N=16)	0.92
MDT contralateral	-1.3 ± 1.6 (N=20)	-1.1 ± 1.6	0.84 ± 1.5	0.2 ± 0.83 (N=16)	0.27
MPT affected	0.1 ± 1.7 (N=21)	0.03 ± 1.4	0.6 ± 1.2	0.6 ± 1.6 (N=16)	0.17
MPT contralateral	0.5 ± 1.3 (N=21)	0.4 ± 1.4	0.7 ± 0.9	0.3 ± 1.5 (N=16)	0.46
PPT affected	1.4 ± 1.1 (N=21)	1.3 ± 0.8	0.7 ± 1.2	-0.6 ± 1.3 (N=15)	0.12
PPT contralateral	1.1 ± 1.1 (N=21)	1.1 ± 0.9	0.8 ± 1.1	-0.4 ± 0.9 (N=15)	0.15
PPT sternum	1.4 ± 1.2 (N=21)	1.2 ± 1.1	0.8 ± 1.0	-0.4 ± 0.9 (N=15)	0.07

1	<i>von Frey ongoing</i>	2.2 ± 2.5 (N=21)	2.1 ± 2.5	3.6 ± 2.7	1.6 ± 2.8 (N=17)	0.04
2	<i>von Frey sharpness</i>	2.1 ± 2.3 (N=21)	2.1 ± 2.1	1.3 ± 2.4	-0.9 ± 2.7 (N=17)	0.19
<hr/>						
3	Intention-to-treat AO	Baseline	Baseline (pair)	Follow-up	Difference	Paired t-test p
4	OSS	29.1 ± 7.7 (N=24)	30.1 ± 7.0	36.0 ± 6.04	5.9 ± 8.8 (N=21)	0.006
5	PPI	3.6 ± 2.5 (N=24)	4.1 ± 2.3	1.6 ± 2.2	-2.5 ± 2.1 (N=21)	0.0000
6	PD-Q	10.1 ± 6.0 (N=24)	9.9 ± 6.2	6.3 ± 3.9	-3.6 ± 6.4 (N=21)	0.02
7	HADS	11.1 ± 6.7 (N=24)	10.6 ± 6.9	9.0 ± 5.6	-1.6 ± 4.4 (N=21)	0.11
8	<i>MDT affected</i>	-0.8 ± 1.9 (N=24)	-0.8 ± 1.8	-1.1 ± 1.8	-0.3 ± 1.2 (N=21)	0.21
9	<i>MDT contralateral</i>	-0.7 ± 1.5 (N=24)	-0.7 ± 1.5	-1.2 ± 1.6	-0.4 ± 1.6 (N=21)	0.23
10	<i>MPT affected</i>	-0.4 ± 1.1 (N=24)	-0.3 ± 1.1	-0.008 ± 1.3	0.3 ± 1.4 (N=21)	0.34
11	<i>MPT contralateral</i>	-0.2 ± 1.3 (N=24)	-0.2 ± 1.3	-0.1 ± 1.3	0.05 ± 1.3 (N=21)	0.86
12	<i>PPT affected</i>	0.6 ± 1.0 (N=16)	0.6 ± 1.1	0.3 ± 1.0	-0.3 ± 1.2 (N=12)	0.39
13	<i>PPT contralateral</i>	0.8 ± 1.0 (N=17)	0.9 ± 1.0	0.5 ± 0.9	-0.5 ± 1.1 (N=13)	0.16
14	<i>PPT sternum</i>	0.6 ± 0.9 (N=17)	0.7 ± 0.94	0.6 ± 0.8	-0.1 ± 0.8 (N=13)	0.64
15	<i>von Frey ongoing</i>	2.0 ± 2.4 (N=24)	2.3 ± 2.4	2.8 ± 1.8	0.5 ± 2.8 (N=21)	0.39
16	<i>von Frey sharpness</i>	2.2 ± 2.4 (N=23)	2.4 ± 2.5	1.8 ± 2.4	-0.6 ± 2.3 (N=21)	0.22
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17	Intention-to-treat	Baseline	Baseline	Follow-up	Difference	Paired t-test p
18	AMSR		(pair)			
19	OSS	26.7 ± 8.0 (N=21)	26.3 ± 7.8	31.1 ± 11.5	4.8 ± 6.3 (N=16)	0.008
20	PPI	2.7 ± 2.4 (N=21)	2.8 ± 2.6	3.3 ± 3.6	0.5 ± 2.0 (N=16)	0.33
21	PD-Q	10.5 ± 5.9 (N=21)	10.1 ± 5.8	8.8 ± 6.5	-1.3 ± 5.2 (N=16)	0.35
22	HADS	11.4 ± 8.6 (N=21)	11.3 ± 9.1	11.8 ± 9.7	0.5 ± 4.8 (N=16)	0.68
23	<i>MDT affected</i>	-1.0 ± 1.7 (N=20)	-1.1 ± 1.6	-1.7 ± 1.9	-0.6 ± 1.4 (N=16)	0.12
24	<i>MDT contralateral</i>	-1.4 ± 1.9 (N=20)	-1.5 ± 1.8	-1.6 ± 1.8	-0.07 ± 1.2 (N=16)	0.83
25	<i>MPT affected</i>	0.5 ± 1.0 (N=21)	0.5 ± 1.1	0.4 ± 0.9	-0.08 ± 1.5 (N=16)	0.85
26	<i>MPT contralateral</i>	0.3 ± 1.0 (N=21)	0.5 ± 1.0	0.7 ± 0.8	0.2 ± 1.1 (N=16)	0.45
27	<i>PPT affected</i>	1.1 ± 1.4 (N=19)	0.9 ± 1.5	0.6 ± 1.2	-0.4 ± 1.4 (N=14)	0.34
28	<i>PPT contralateral</i>	0.7 ± 1.1 (N=19)	0.5 ± 1.1	0.5 ± 1.1	0.06 ± 1.3 (N=14)	0.87
29	<i>PPT sternum</i>	1.2 ± 1.0 (N=19)	1.1 ± 1.1	0.6 ± 1.1	-0.4 ± 1.0 (N=14)	0.14
30	<i>von Frey ongoing</i>	2.6 ± 3.2 (N=19)	2.4 ± 3.1	2.3 ± 3.3	-0.03 ± 1.8 (N=16)	0.95
31	<i>von Frey sharpness</i>	3.5 ± 2.4 (N=18)	3.2 ± 2.3	3.7 ± 2.5	0.5 ± 4.0 (N=15)	0.61

The QST values are analysed as reversed Z-scores. No age and sex in the regression model.

Table 3 - Between-arm changes in clinical and psychophysical measures

ITT	ASAD vs AO	ASAD vs AMSR	AO vs AMSR
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Outcomes	MD (95% CI) [p-value]	MD (95% CI) [p-	MD (95% CI) [p-value]
		value]	
OSS	0.92 (-4.78, 6.61)	4.05 (-1.76, 9.86)	3.13 (-2.75, 9.02)
PPI	0.92 (-0.60, 2.44)	-1.82 (-3.29, -0.34)	-2.74 (-4.26, -1.22)
PD-Q	0.16 (-2.8, 3.1)	-1.73 (-4.79, 1.33)	-1.46 (-5.25, 0.84)
HADS	-1.2 (-4.88, 2.48)	-3.65 (-7.45, 0.15)	-2.45 (-6.24, 1.34)
<i>MDT affected</i>	-0.1 (-0.38, 0.18)	-0.22 (-0.51, 0.070)	-0.12 (-0.40, 0.16)
<i>MDT contralateral</i>	-0.14 (-0.39, 0.11)	-0.16 (-0.42, 0.10)	-0.017 (-0.27, 0.24)
<i>MPT affected</i>	-0.17 (-0.44, 0.11)	-0.054 (-0.33, 0.22)	0.090 (-0.19, 0.36)
<i>MPT contralateral</i>	-0.19 (-0.43, 0.05)	0.020 (-0.23, 0.27)	0.21 (-0.032, 0.46)
<i>PPT affected</i>	-0.67 (-0.21, 0.08)	-0.023 (-0.15, 0.11)	0.044 (-0.10, 0.19)
<i>PPT contralateral</i>	-0.05 (-0.16, 0.07)	0.0079 (-0.11, 0.12)	0.053 (-0.067, 0.17)
<i>PPT sternum</i>	0.029 (-0.079, 0.14;)	-0.009 (-0.11, 0.09)	-0.038 (-0.15, 0.07)
<i>von Frey ongoing</i>	-0.19 (-1.65, 1.27)	-0.93 (-2.43, 0.58)	-0.74 (-2.22, 0.74)
<i>von Frey sharpness</i>	0.64 (-0.96, 2.24)	0.039 (-1.67, 1.75)	-0.60 (-2.27, 1.08)

The QST values are log-transformed. Age and sex in the model

Predictive value of QST and expectations

Better function and pain at the follow-up (higher OSS) was associated with lower pain ratings during the baseline assessment (baseline PPI: $\beta=-1.1479$, 95%CI -2.24 to -0.032) and lower pain threshold on the affected side (logMPT: $\beta=-6.5980$, 95%CI -12.64 to -0.54) and higher pain threshold for pressure pain contralateral side (logPPT: $\beta=15.4427$, 95%CI 2.29 to 28.59). Expectations did not predict OSS at the follow-up (for high expectations: $\beta=2.51$, 95%CI: -3.48 to 8.50 and for very high expectations $\beta=2.65$, 95%CI -2.92 to 8.22).

Neuroimaging

Out of 67 patients recruited into the neuroimaging study, there were no MRI data for five patients: one patient had unexpected findings on MRI, one was claustrophobic, one was in too much pain and stopped the scan, and two patients could not be scanned because of medical implants. Also one healthy control subject had incidental findings and one could not be scanned because of dental implants. This left 62 patients and 22 healthy controls for the analysis.

Activation in the patient group at baseline

At baseline, brain activation in response to von Frey stimulation negatively correlated with the strength of stimulus in the ipsilateral cluster including postcentral/supramarginal gyrus/central operculum/supramarginal gyrus, the ipsilateral amygdala/parahippocampal gyrus/temporal pole, and the contralateral postcentral/supramarginal gyrus (Figure 4).

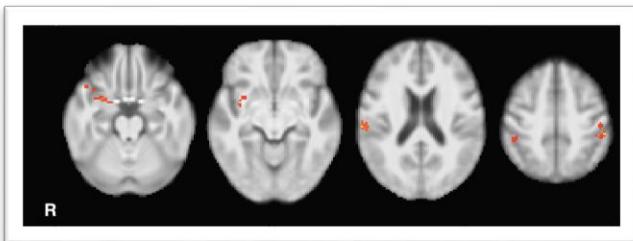


Figure 4 - Correlations between brain activation and logMDT in patients

One-group analysis with age and sex as covariates of no interest. FEAT analysis with cluster forming threshold $Z=3.1$ and $p=0.05$. Clusters of activation in the ipsilateral postcentral gyrus, central operculum and supramarginal gyrus ($Z_{max}=6.37$, coordinates: 66, -20, 19), the ipsilateral amygdala/parahippocampal gyrus/temporal pole ($Z_{max}=4.32$, coordinates: 29, 6, -21), the contralateral postcentral/supramarginal gyrus ($Z_{max}=6.02$, coordinates: -51, -40, 52), and the ipsilateral postcentral/supramarginal gyrus ($Z_{max}=4.61$, coordinates: 47, -37, 54).

When also ongoing pain and stimulus ratings were entered into the analysis, logMDT correlated negatively with activation in the somatosensory regions: ipsilateral operculum, and supramarginal/postcentral gyrus (Figure 5 A), von Frey sharpness ratings correlated positively with activation in the contralateral anterior insula and frontal operculum (Figure 5 B), and ratings for ongoing pain during stimulation correlated negatively with activation in the anterior cingulate/paracingulate gyrus and in the contralateral frontal pole (Figure 5 C).

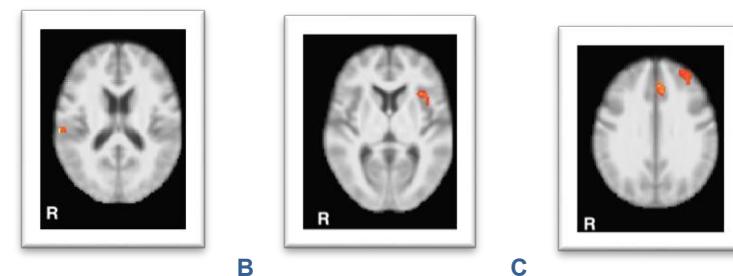


Figure 5 – Correlations between brain activation, MDT, sharpness ratings and pain ratings

One-group analysis with age and sex as covariates of no interest. FEAT analysis with cluster forming threshold $Z=3.1$ and $p=0.05$. A. negative correlation with logMDT in the ipsilateral operculum, supramarginal/postcentral gyrus, ($Z_{max}=4.62$, coordinates: 65, -20, 16); B. positive correlation with ratings for von Frey sharpness in the contralateral anterior insula/frontal operculum ($Z_{max}=5.39$, coordinates: -35, 18, 5); C. negative correlation between ongoing pain ratings and the anterior cingulate/paracingulate gyrus ($Z_{max}=6.25$, SYM coordinates: -2, 28, 38 and the contralateral frontal pole ($Z_{max}=5.49$, coordinates: -21, 49, 42).

Differences between the patient and control group

The activation pattern in response to von Frey stimulation was similar in patients and in controls. An unpaired t-test between stimulus-evoked activation in the patient and in the control group, with age and sex as covariates of no interest, showed more activation in the control group in the ipsilateral secondary somatosensory cortex/parietal operculum/postcentral gyrus, contralateral superior frontal gyrus, and ipsilateral precentral gyrus/superior frontal gyrus (Figure 6).

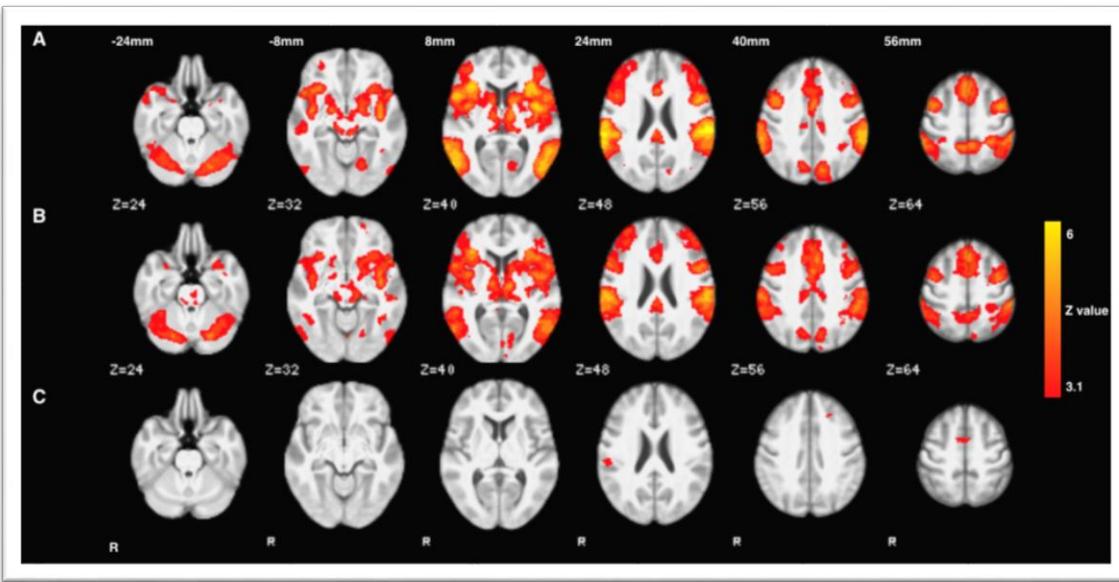


Figure 6 – Brain activation in the patient and control group and differences between groups

Unpaired group analysis with age and sex as covariates of no interest. FEAT analysis with cluster forming threshold $Z=3.1$ and $p=0.05$. A. mean activation in the patient group ($N=62$); B. mean activation in the control group ($N=22$); C. more activation in the control group in the ipsilateral secondary somatosensory cortex/parietal operculum/postcentral gyrus ($Z_{max}=4.48$, coordinates: 58, -24, 20), contralateral superior frontal gyrus ($Z_{max}=4.69$, coordinates: -16, 34, 36), and ipsilateral precentral gyrus/superior frontal gyrus ($Z_{max}=3.84$, coordinates: 28, -12, 59).

Treatment effect – intention to treat analysis

In a PALM analysis using the 2-level models all results were subthreshold.

In a 2-level analysis (Appendix – 2-level model - design 1) using FEAT the only region showing significant between-arm effect in a second-level analysis (F-test, design1, $Z=3.1$) was in the superior frontal/paracingulate gyrus (Figure 7 A). (An ROI analysis in a 5mm sphere in this region (a peak in: 0, 27, 51) has shown significant reduction of activation in the AO arm $t=2.6766$, $p=0.0145$ and an increase in the ASAD arm $t=-3.5740$, $p=0.0025$) but no significant change in the AMSR arm.)

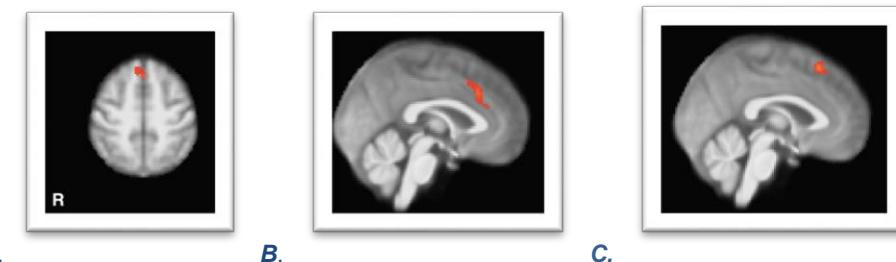


Figure 7 – Between-arm effect on stimulus-evoked brain activation – 2-level, design 1 between groups

2-level analysis. FEAT analysis with cluster forming threshold $Z=3.1$ and $p=0.05$. A. F-test: (AO, bl>fu) > (ASAD, bl>fu) AND (ASAD, bl>fu) > (AMSR, bl>fu) ($Z_{max}=4.01$, Coordinates: 0, 27, 51); B. treatment effect fu>bl, $Z_{max}=4.01$, Coordinates: (Zmax=4.01, Coordinates: 1, 25, 37); C. treatment effect (AO, bl>fu) > (ASAD, bl>fu), $Z_{max}=4.28$, Coordinates: 0, 25, 52 [at Z=2.3 also angular/superior parietal lobule].

There was an increase of activation at the follow-up, across the arms, in the paracingulate/anterior cingulate cortex and no effect for the opposite contrast, at neither threshold (Figure 7 B). (An ROI analysis in a 5mm sphere in this region (peak

in 1, 25, 37) has shown no significant effect in the AO arm ($p=0.419$), but a significant increase in signal in the ASAD arm ($t = -2.5675$ $p=0.0207$) and a significant increase in the AMSR arm ($t=-3.7501$, $p=0.0019$).

There was a significantly larger difference in the effect in the placebo arm than in the surgical arm (AO, $bl>fu$) > (ASAD, $bl>fu$) in the paracingulate gyrus/superior frontal gyrus, i.e., similar cluster as the F-test results (Figure 7 C).

The difference between changes in placebo and non-interventional arm (AO, $bl>fu$) > (AMSR, $bl>fu$) was significant only at $Z=2.3$ and the local maximum was in the precuneus/posterior cingulate cortex/postcentral gyrus ($Z_{max}=3.97$, coordinates: 19, -56, 12 and $Z_{max}=4.29$, coordinates 11, -44, 53). Differences in changes for other contrasts were not significant neither at $Z=3.1$ nor at $Z=2.3$.

There was no significant effect in the between-arms design (Design 2) neither at $Z=3.1$ nor at $Z=2.3$.

Post-hoc analysis

A paired t-test in the placebo arm (AO) showed a reduction of activation at the follow-up in the inferior parietal lobule, with no increase of activation (Figure 8 A).

In the surgical arm (ASAD), there was no reduction of activation and an increase of activation at the follow-up in the paracingulate cortex/anterior cingulate cortex (Figure 8 B).

In the non-interventional arm (AMSR), there was also no reduction of activation and an increase of activation in the paracingulate cortex/anterior cingulate cortex as well as in the precentral/postcentral gyrus and supramarginal gyrus (Figure 8 C).

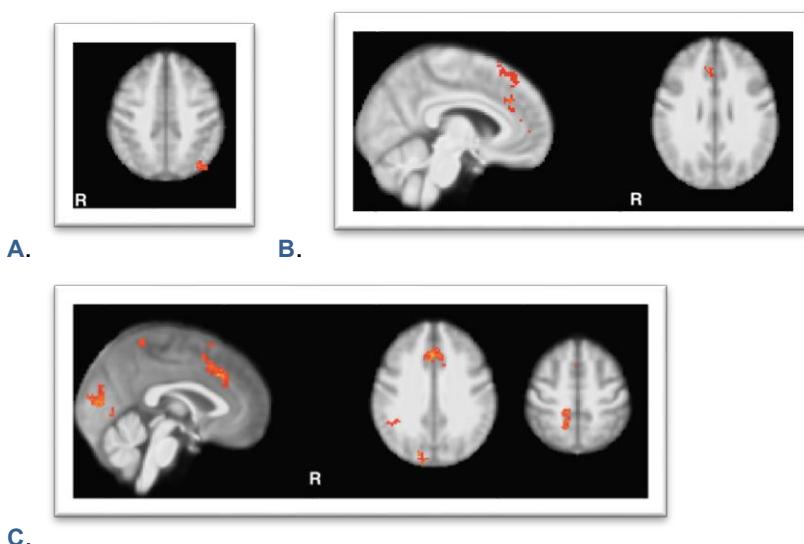


Figure 8 – Treatment effect within-arm

Paired t-test within each arm. FEAT analysis with cluster forming threshold $Z=3.1$ and $p=0.05$. A. AO arm, $bl>fu$, the contralateral inferior parietal lobule ($Z_{max}=4.29$, coordinates: -33, -74, 45), with no increase of activation; B. ASAD arm, $fu>bl$, in the paracingulate cortex/anterior cingulate cortex ($Z_{max}=4.46$, coordinates: 5, 34, 34); C. AMSR arm, $fu>bl$, in the paracingulate cortex/anterior cingulate cortex ($Z_{max}=5.18$, coordinates: 1, 25, 37) as well as in the ipsilateral precentral/postcentral gyrus ($Z_{max}=4.65$; coordinates: 9, -37, 54) and supramarginal gyrus ($Z_{max}=4.65$, coordinates: 9, -37, 54).

The paired t-test was also run with ratings for sharpness and ongoing pain in the model. In the placebo arm (AO), there was no treatment effect and no correlation with ratings for ongoing pain but ratings for sharpness correlated positively with activation in the ipsilateral inferior frontal gyrus/pars opercularis (Figure 9 A).

In the surgical arm (ASAD), there was no significant treatment effect and no correlation with ratings for sharpness. Ongoing pain rating correlated negatively with the activation in the paracingulate/anterior cingulate cortex (Figure 9 B).

In the non-interventional arm (AMSR), no regions correlated with ratings for ongoing pain, and ratings for sharpness correlated positively with activation in the ipsilateral hippocampus/amygdala (Figure 9 C).

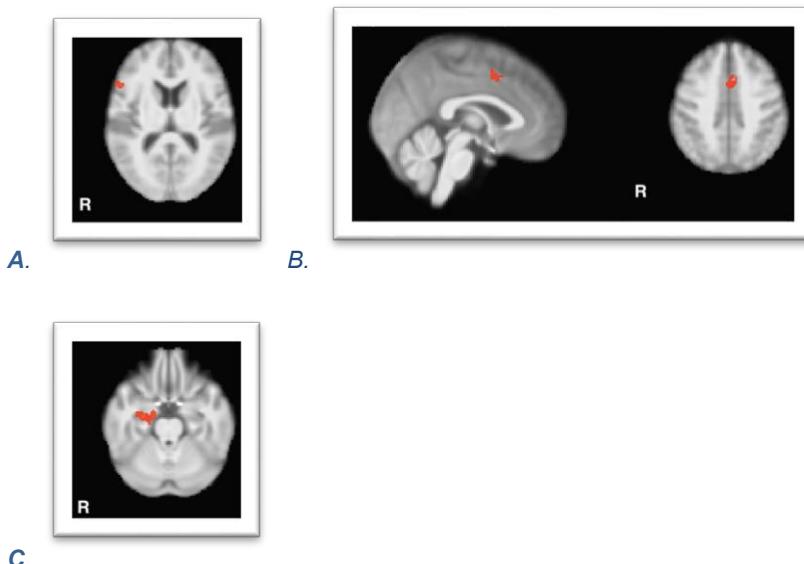


Figure 9 - Treatment effect on stimulus-evoked brain activation related to sharpness and pain – between-groups effect

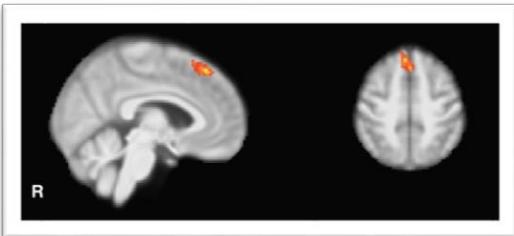
Paired t-test within each arm with ratings for von Frey sharpness and ongoing pain as covariates. FEAT analysis with cluster forming threshold Z=3.1 and p=0.05. A. AO arm positive correlation with ratings for sharpness the ipsilateral inferior frontal gyrus/pars opercularis (Zmax=3.93 coordinates: 56, 19, 12) (at Z=2.3 more frontal extensive activation within the frontal lobe); B. ASAD arm, negative correlation with ratings for ongoing pain the paracingulate, anterior cingulate cortex Zmax =3.61, coordinates: -1, 11, 46 (at Z=2.3 also activation bilaterally in the insular/operculum and in the brainstem); C. AMSR arm, positive correlations with ratings for sharpness the ipsilateral hippocampus/amygdala, Zmax=3.97 coordinates: 26, -10, -23 (at Z=2.3 also activation in somatosensory cortex).

Sensitivity analysis

Treatment effect was also analysed using a 3-level model. The F-test of differences between the arms resulted in a significant cluster in the contralateral superior frontal gyrus/paracingulate gyrus (Figure 10 A).

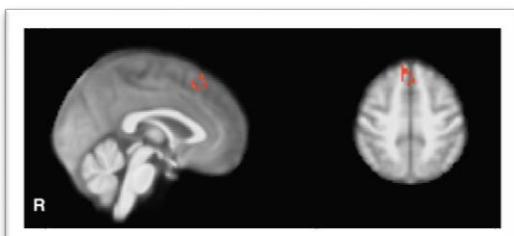
The only significant between-arm difference in treatment effect was between the placebo and surgical arm with the significant cluster was located in the ipsilateral superior frontal gyrus/premotor cortex (Figure 10 B).

A. F-test



B. AO(bl>fu) > ASAD(bl>fu)

Figure 10 – Treatment effect on stimulus-evoked brain activation – between arms



Unpaired group analysis with age and sex as covariates of no interest. FEAT analysis with cluster forming threshold Z=3.1 and p=0.05. A. F-test of effect across the arms. Significant cluster in the contralateral superior frontal gyrus/paracingulate gyrus, Zmax=4.16; Coordinates: -1, 24, 51); B. difference in effect between AO and ASAD: (AO, bl>fu) > (ASAD, bl>fu), Zmax=5.89, Coordinates: 4, 33, 52).

Within the placebo arm, there was a reduction of activation between baseline and follow-up in the contralateral inferior parietal lobule (Figure 11 A). There was no significant effect for the opposite contrast.

In the ASAD arm, there was an increase of activation between baseline and follow-up in the ipsilateral superior frontal gyrus/premotor cortex (Figure 11 B) (at Z=2.3 local maximum was in the ipsilateral paracingulate/anterior cingulate cortex. There was no reduction in activation.

In the surgical arm, there was an increase of activation in the ipsilateral premotor cortex/juxtapositional lobule, the paracingulate/anterior cingulate cortex, ipsilateral precuneus, ipsilateral pre- and postcentral gyrus, and the occipital cortex (Figure 11 C).

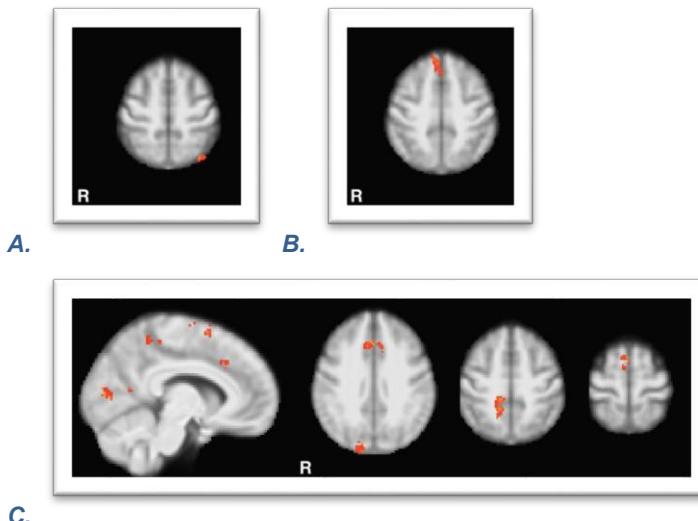


Figure 11 – Treatment effect on stimulus-evoked brain activation – within arms

3-level analysis. FEAT analysis with cluster forming threshold Z=3.1 and p=0.05. **A.** treatment effect in the AO arm, bl>fu, in the contralateral inferior parietal lobule, Zmax=4.68, Coordinates: -32, -72, 56 ; (at Z=2.3 also contralateral inferior frontal gyrus Zmax=4.26, Coordinates: -49,35, 10 , and cerebellum Zmax=3.95, Coordinates: 38, -76, -35) **B.** treatment effect in the ASAD arm, fu>bl, in the ipsilateral superior frontal gyrus/premotor cortex (Zmax=4.52, Coordinates:4, 33, 52), (at Z=2.3 local maximum was in the ipsilateral paracingulate/anterior cingulate cortex, Zmax=4.63, Coordinates: 6, 33, 34); **C.** treatment effect in the AMSR arm, fu>bl, in the ipsilateral premotor cortex/juxtapositional lobule (Zmax=5.2, Coordinates:3, 4, 66), paracingulate/anterior cingulate cortex (Zmax=5.1, Coordinates: 2, 27, 39), ipsilateral precuneus (Zmax=4.7, Coordinates: 16, -54, 12), ipsilateral pre- and postcentral gyrus (Zmax=4.6, Coordinates:9, -35, 52), and the occipital cortex (Zmax=5.8, Coordinates:14, -67, 11 and Zmax=5.29, Coordinates:20, -81, 32)

Difference in the effect between the surgical and non-interventional was significant only at Z=2.3 and the effect was present in the ipsilateral pre- and postcentral gyrus and ipsilateral occipital cortex. Also difference between change in the placebo and the non-interventional arm (AO, bl>fu) > (AMSR, bl>fu) was significant only the lower threshold in the paracingulate/posterior cingulate gyrus, superior frontal gyrus, middle frontal gyrus, and the occipital cortex. There was no significant effect for other contrasts.

DISCUSSION

(Word limit 1500, currently 2600)

Summary of the main findings

Patients with rotator cuff tendinopathy demonstrated symptoms of bilateral hypoesthesia to light touch (MDT) and bilateral allodynia in response to deep pressure (PPT); the latter more pronounced on the affected side. Worse OSS scores were associated with hypoesthesia and allodynia on the affected side, high expectations as well as high PD-Q scores.

After treatment, there was a significant improvement in OSS in all trial arms without differences between arms and an improvement in pain (PPI) in the placebo arm only with were significant differences in the effect between the arms. We did not observe treatment effect on any of the QST values.

In neuroimaging, there was more stimulus-evoked activation in the control group, mainly in the somatosensory regions. In the patient group, hypoesthesia was associated with less activation in the somatosensory cortex, ratings for sharpness of the stimulus correlated positively with activation in the contralateral anterior insula,

1 while ratings for pain during the stimulation correlated negatively with activation in the
2 anterior cingulate/paracingulate gyrus.
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4 Across the arms, treatment effect was present in the contralateral superior frontal
5 gyrus/paracingulate gyrus (medial frontal cortex) and the only significant between-arm
6 difference in the treatment effect was between the placebo and the surgical arm.
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8 In the surgical arm there was an increase of activation in the paracingulate cortex/
9 cingulate cortex, in the placebo arm there was a reduction of activation in the inferior
10 parietal lobule, and in the non-interventional arm there was an increase of activation
11 in the paracingulate cortex/ cingulate cortex as well as in the precentral/postcentral
12 and supramarginal gyrus.
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15 Sharpness of the stimulus correlated positively with activation in the inferior frontal
16 cortex/operculum and in the non-interventional arm with the activation in the
17 amygdala/hippocampus.
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20 Strengths and Limitations 21

22 This is a unique extension to an interventional RCT. It incorporated not only clinical
23 and psychological assessment but also QST and neuroimaging, which helped to
24 investigate what mechanisms may possibly explain observed clinical effects. The
25 strength of this study lies in the design, which included both comparison between
26 patients and pain-free controls as well as follow-up analysis comparing the effect of
27 surgery with placebo surgery and non-interventional management. Results of this
28 study are generalizable because the participants were representative for patients with
29 rotator cuff tendinopathy and they underwent a popular arthroscopic treatment or
30 standard conservative management.
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33 Although, the patient group in this study is four times larger than in the previous QST
34 paper on shoulder pain [28], it was smaller than the one calculated in the power
35 analysis which limited our ability to detect the true effect. The neuroimaging part was
36 only added at one of the centres recruiting into CSAW which limited the number of
37 potential participants. 80% of patients recruited into CSAW from the Oxford centre
38 participated in the neuroimaging study, but the required sample size was not reached
39 at baseline and patient attrition and unavailable/poor quality data further reduced the
40 sample size of at the follow-up to about 66% of the necessary size. Furthermore,
41 during this trial, the recommended minimum cluster-forming threshold in functional
42 analysis was changed from $Z=2.3$ to $Z=3.1$, for which this study has not been
43 powered.
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46 The limitation for QST assessment was a lack of a population-based referential
47 dataset for shoulder QST values in middle aged individuals. In order to present
48 results as Z-scores the referential values had to be estimated from the control group.
49 Therefore, we presented Z scores to help interpretation of results, but for analyses,
50 we used log-transformed raw values corrected for age and sex. Investigating the
51 effect of treatment on QST profile was difficult because the number of patients
52 available at the follow-up was small and only about a quarter had abnormal QST
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values, which meant that in each trial arm there were fewer than five patients with sensory abnormalities.

Also effect of expectations was difficult to estimate because the patients had generally positive expectations regarding effects of participating in the trial, which was possibly a selection bias; therefore, we could only compare patients with moderately positive expectations to patients with high and very high expectations.

The von Frey monofilament was not perceived as painful and it was also not rated as very sharp. Therefore, the stimulus-evoked brain activation reflects processing of sensory stimuli rather than pain as such. This stimulus has been chosen because it has been used in earlier neuroimaging studies on central sensitisation.[76][27] The probes used for MPT or PPT assessment could not have been used due to possible prolonged pain after stimulation and problems with creating a pain-free baseline for the BOLD experiment and because the device was not MRI safe so it could not be used on patient's shoulder in the scanner.

Differences in pain ratings were not investigated because they may be misleading as a value of 2 may represent both change from 8 to 6 as well as from 2 to 0; therefore, individual pain ratings at baseline and follow-up were used to explain treatment-related brain activation in each arm.

Interpretation

Results of this study suggest that pain in rotator cuff tendinopathy is caused by peripheral and central mechanisms, as QST scores beyond normal range have been present on the affected and the contralateral side. Ipsilateral QST abnormalities correlated with OSS scores but contralateral QST values were associated with paraesthesiae/dysesthesiae and radiating pain.

Our study suggests that neuropathic component was present only in some patients as 66% of the patients had PD-Q scores below 12 which meant that neuropathic component is unlikely. However, 81% of patients reported radiating pain and 48% reported paraesthesiae/dysesthesiae and these sensory disturbances were associated with lower PPT on the contralateral side suggesting central mechanism. Moreover, lower PPT on the contralateral side was a predictor of worse outcome at the follow-up. An earlier study on arthroscopy on shoulder pain also reported that pre-op PD-Q or MPT did not correlate with post-op OSS (only after using a median split MPT showed a predictive value).[28]

Presence of neuropathic changes in tendinopathies, including shoulder impingement, has been reported before [71] [28] [61]. However, it is possible that some of the neuropathic symptoms were caused by cervical radiculopathy, as although, known radiculopathy was an exclusion criterion, it was formally investigated.

We observed bilateral MDT changes and changes on the affected side correlated with OSS. MDT reflects changes in the function of A- β and, to a lesser degree, A- δ fibres.[68] Loss of input from A- β fibres may diminish the inhibition of the projecting

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neurons and cause a “low input” pain.[46] Bilateral hypoesthesia has been described
in patellofemoral pain syndrome [35]. Hypoesthesia has been interpreted as a sign of
altered sensory processing indicating central sensitisation.[65]

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MPT hyperalgesia, which reflects central sensitisation of the A- δ input [72] was not
observed in our study. It was reported in patients with tendinopathy [28] [72];
although, these studies did not account for age and sex in the analyses, which could
have led to different results.

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As for PPT, we observed lower values on both sides, with differences between the
affected and the contralateral side. Presence of bilateral mechanical allodynia has
been reported by several studies on tendinopathy [53] [52] [11] [12] [23] and also
used as a predictor to identify patients with tendinopathy.[40] In our study, low PPT
values on the affected side were associated with worse OSS values and low PPT
values on the contralateral side were associated with presence of radiating pain and
paraesthesiae/dysesthesiae. PPT reflects pressure sensitivity, mainly static
mechanical allodynia of deeper tissues [39] [68] and it has been interpreted as a
manifestation of central sensitisation [53]. However, in shoulder pain [23] and in most
chronic musculoskeletal pain conditions[24] [62] it is probably caused both by central
and peripheral sensitisation.

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We did not observe any treatment effect on QST measures. This may be explained
by a small number of patients at the follow-up and small number of patients
demonstrating abnormal QST. Due to a small sample size and presence of QST
changes in about a quarter of patients we may not have the necessary power to
detect a change. It is also possible that QST is not sensitive enough to detect a
change. As more standardized than simple pain ratings, QST were suggested to
improve assessment of pain and treatment efficacy and also to predict treatment
outcomes.[15] However, this has not always been demonstrated[8] and a recent
meta-analysis showed very little or no correlation between QST values and pain[31]

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OSS scores improved significantly in all three arms but there were no differences
between arms in this patient sample. Pain intensity (PPI) reported during the follow-
up visit improved in the placebo arm but not surgical (0.07) and non-interventional
arm and there was a significant between-group treatment effect. In an earlier open-
label study on ASAD for shoulder pain there was a significant improvement in OSS
and pain ratings.[28]

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Pain ratings (PPI at baseline) did not correlate with QST which was unexpected but
was in line with findings of a recent meta-analysis [31] which reported that QST
markers of central sensitisation did not correlate with pain reports. Pain ratings seem
to be a proxy for dissatisfaction with treatment and distress rather than a marker for
disease severity. While OSS improved in all trial arms, without differences between
the arms, pain ratings improved in the placebo arm, showed a trend for improvement
in the surgical arm, and did not change in the non-interventional arm.

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Expectations are a key component of placebo response [37] and may be a
confounder in assessing outcome of clinical trials.[10,45] In an earlier study

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6 preoperative expectations correlated with self-assessed outcomes in rotator cuff
7 surgery[30] but in this study expectations did not predict OSS at the follow-up. This
8 may be because patients generally had positive expectations which limited the
9 analysis.
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15 Depression and anxiety mediate the relationship between pain and disability [42] and
16 may explain the lack of correlation between objective measures and subjective pain
17 reports in musculoskeletal pain [13] In our study, HADS explained OSS in univariate
18 but not in multivariate analysis and did not predict OSS at the follow-up. Earlier
19 studies showed that patients with higher levels of depression and anxiety need larger
20 improvement to report that the treatment was a success[75] but have higher rates of
21 placebo response.[70]
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24 Better function and pain at the follow-up was predicted by lower pain ratings (PPI)
25 during the baseline assessment, lower pain threshold (MPT) on the affected side and
26 higher pain threshold for pressure pain (PPT) on the contralateral side An earlier
27 study on arthroscopy on shoulder pain also reported that pre-op PD-Q or MPT did not
28 correlate with post-op OSS (only after using a median split MPT showed a predictive
29 value).[28]

30 Brain activation pattern was similar in patients and in controls, with stronger activation
31 in the somatosensory regions in the control group. In the patient group, MDT scores
32 correlated with activation in somatosensory regions, which reflected hypoesthesia,
33 i.e., patients did not perceive weaker stimuli. This confirms the psychophysical
34 findings of relatively small differences in QST scores between the groups and
35 presence of hypoesthesia in the patient group. These differences suggest modulation
36 of sensory input in the patient group, possibly reflecting reduced inhibition of pain[46]
37 but we did not observe increased activation in the secondary somatosensory cortex
38 and the brainstem indicating a presence of central sensitisation.[76]

39 When ratings for stimulus sharpness and ongoing pain were analysed in the patient
40 group, sharpness correlated positively with activation in the regions involved in
41 interoception/pain perception.[54] whereas ongoing pain ratings correlated negatively
42 with activation in the regions encoding attention and the affective component of
43 pain.[56][3]
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45 The stimulus-evoked brain activation reflected changes in processing of sensory
46 stimuli rather than pain stimuli. We have investigated changes in ongoing pain using
47 Arterial Spin Labelling, and the comparison between patients and controls was
48 reported previously.[69] In brief, there was a larger perfusion associated with raising
49 of the affected shoulder in patients than in controls in the ipsilateral primary
50 somatosensory cortex, ipsilateral operculum/insular cortex, ipsilateral putamen and
51 bilaterally in the thalamus, midbrain, and the cerebellum.[69] We did investigate the
52 between- and within-arm effect of treatment on ASL perfusion, but there were no
53 significant results because of low signal to noise ratio which is an inherent problem
54 with ASL as well as technical problems during ASL acquisition which resulted in
55 small number of datasets available for the analysis at the follow-up.
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14 Across trial arms, there was a change in activation in the superior
15 frontal/paracingulate gyrus and this effect seemed to be driven by a difference in
16 treatment effect between the placebo and surgical arm. The changes were present in
17 the regions involved in decision making and reward/fear avoidance circuitry [67] rather
18 than typical structures involved in changes in sensory processing, sensitisation, or
19 placebo response[3][64]. The cingulate region, which showed increased activation at
20 the follow-up across all three trial arms, is also associated with reward/avoidance and
21 responds to nociceptive transmission from the thalamus mediating fear and
22 nocifensive behaviour.(according to Vogt this is not a division of anterior cingulate
23 cortex as suggested by the atlas labels)[66]

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25 Within the surgical arm, there was an increase of activation at the follow-up in the
26 paracingulate/midcingulate region, similar to the main treatment effect. In the placebo
27 arm, there was a reduction in activation at the follow-up in the inferior parietal lobule.
28 Reduction of activation in this region has been described in placebo analgesia[1] but
29 this is not one of the key “placebo regions” such as rostral anterior cingulate cortex,
30 medial prefrontal cortex or brainstem. However, this study investigated changes in
31 stimulus-evoked activation approximately three months after surgical placebo
32 intervention in chronic pain population, which may explain differences between
33 findings of this study and results of experimental studies with shorter time between
34 placebo and assessment.

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36 In the non-interventional arm, there was an increase of activation in the paracingulate/cingulate region involved in decision making and nocifensive behaviour
37 as well as in the supramarginal gyrus (i.e., somatosensory association cortex
38 reflecting spatial attention) and ipsilateral sensorimotor cortex, which may be
39 interpreted as changes in processing of the sensory stimulus.

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41 Global within-arm differences did not show the expected reduced nociception and
42 sensitisation after surgery and placebo analgesia after surgical placebo. However,
43 ratings for sharpness correlated with activation in the in the ipsilateral inferior frontal
44 gyrus/pars opercularis and in the non-interventional arm with activation in the
45 right/ipsilateral hippocampus/amygdala, which was reported during a placebo and
46 nocebo condition, respectively.[6] This would suggest that in the placebo arm the
47 ratings were related to cognitive modulation of pain while in the non-interventional
48 group that “lost” in the “randomisation lottery” the ratings were driven by fear and
49 anxiety. The reason why we observed a nocebo effect in the hippocampus but did not
50 observe the placebo effect in the medial prefrontal cortex is because the nocebo
51 effect seems to be more easily induced.[57]

52 Conclusions

53 This a unique study combining QST and neuroimaging assessment with clinical
54 assessment in a surgical randomised controlled trial with a placebo and a non-
55 interventional arm. This study demonstrated that most of the patients with rotator cuff
56 tendinopathy had similar QST scores as pain-free controls and PainDETECT scores
57 suggesting nociceptive pain mechanisms. QST assessment was not very useful in
58 assessing treatment efficacy as the values did not change in any of the trial arms.
59 Brain activation in response to a sensory stimulus was stronger in the control group,
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possibly suggesting descending inhibition. Treatment effect was present in the regions encoding reward/avoidance rather than sensory processes but stimulus ratings correlated with regions involved in placebo response in the placebo arm and with regions involved in nocebo response in the non-interventional arm. This raises the question how much of the placebo/nocebo effect reflect subjective ratings rather than underlying physiological changes in stimulus processing.

10 Abbreviations
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AMSR: Active monitoring with specialist reassessment
ANOVA: Analysis of variance
AO: Arthroscopy only
ASAD: Arthroscopic sub-acromial decompression
CI: Confidence Interval
CSAW: Can Shoulder Arthroscopy Work?
fMRI: Functional magnetic resonance imaging
MRI: Magnetic resonance imaging
OA: Osteoarthritis
OSS: Oxford Shoulder Score
QST: Quantitative sensory testing
RCT: Randomised controlled trial
SD: Standard deviation
PPT: Pressure Pain Threshold
MDT: Mechanical Detection Threshold
MPT: Mechanical Pain Threshold

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2 **Summary:** A QST and neuroimage extension of a randomised controlled surgical trial
3 with a placebo and non-interventional arm, which did not show significant differences
4 between the arms in QST values and somatosensory processing but demonstrated
5 that the placebo/nocebo response reflects subjective stimulus ratings.
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Figure 2

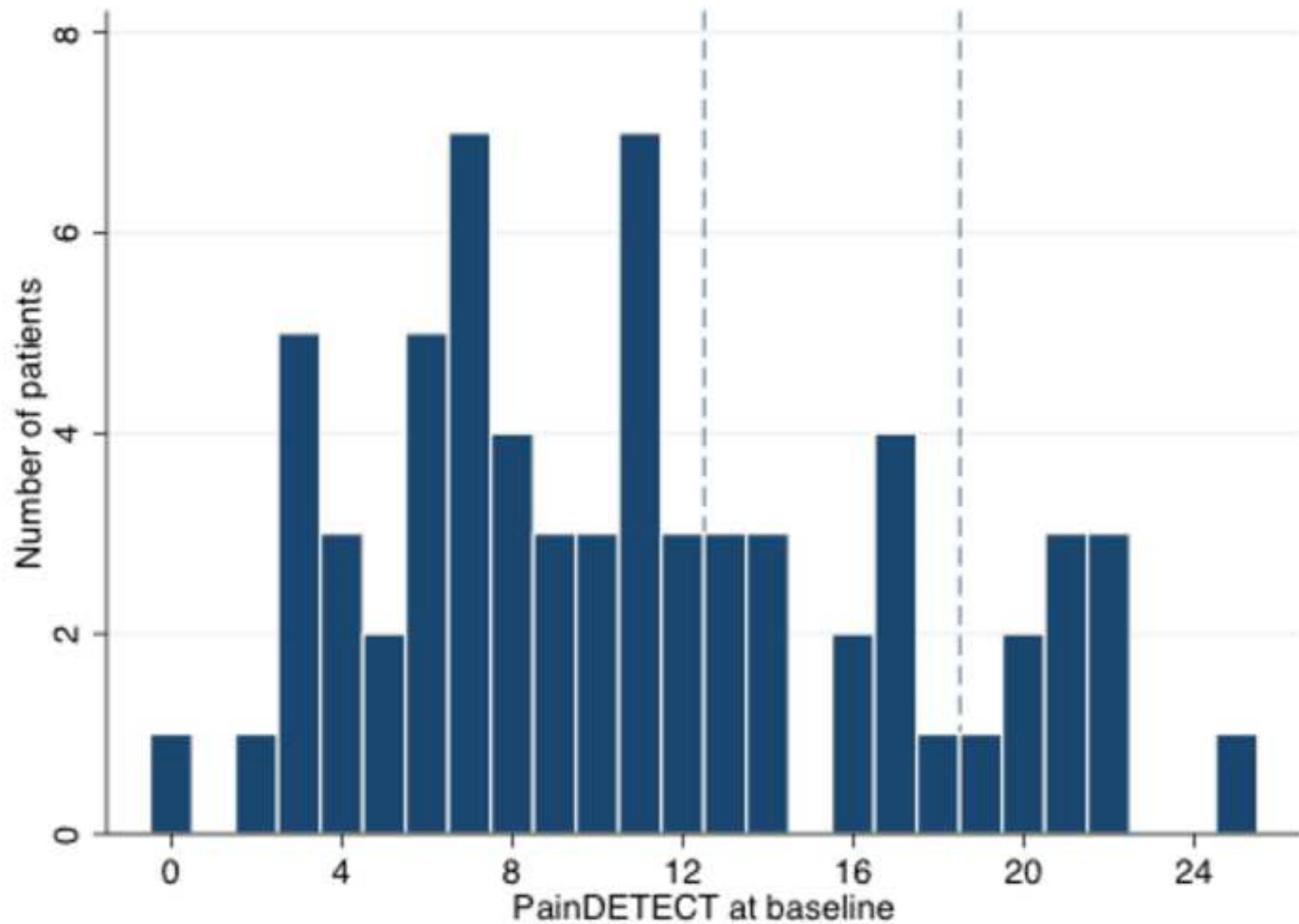
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Figure 3

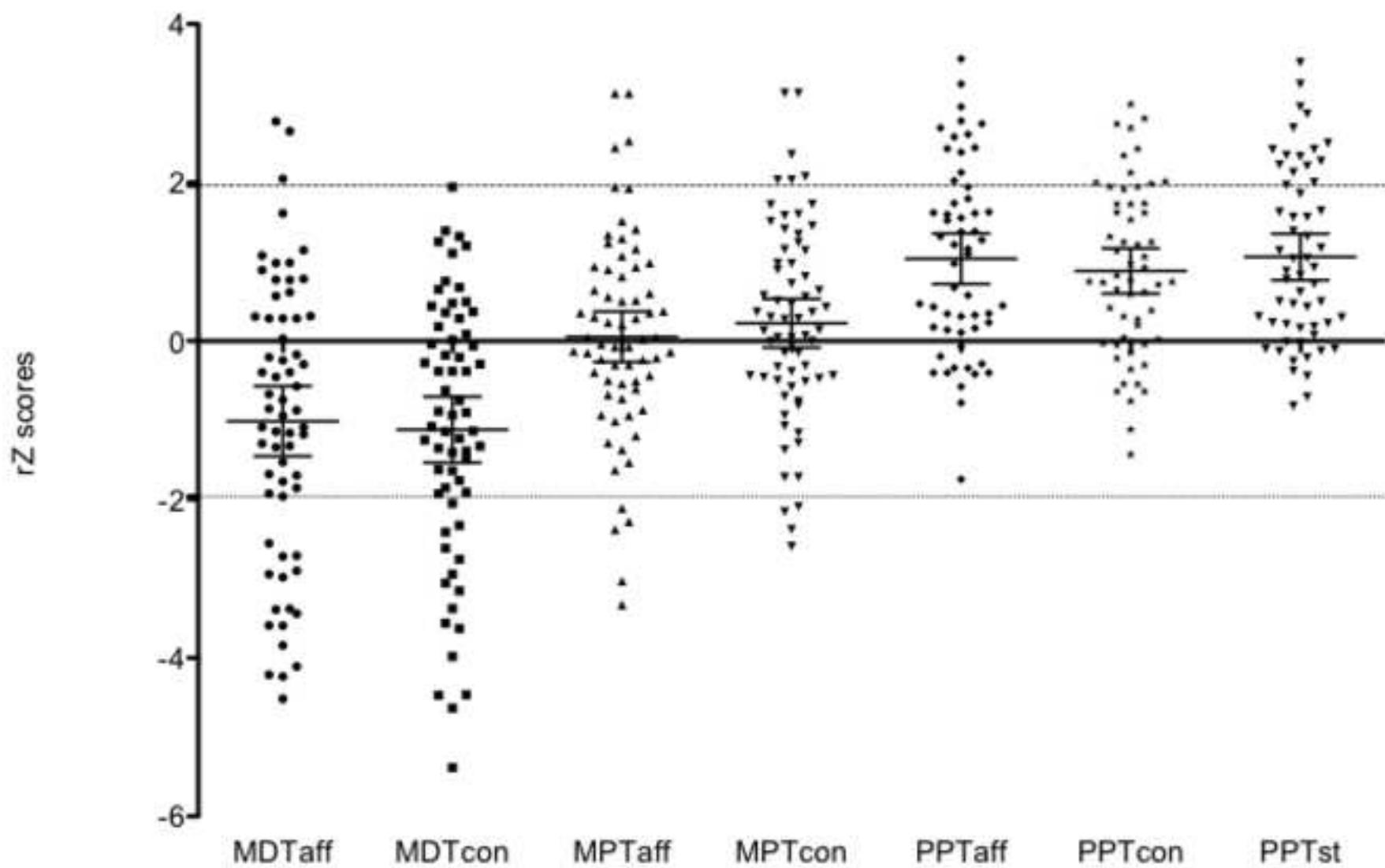
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Figure 4

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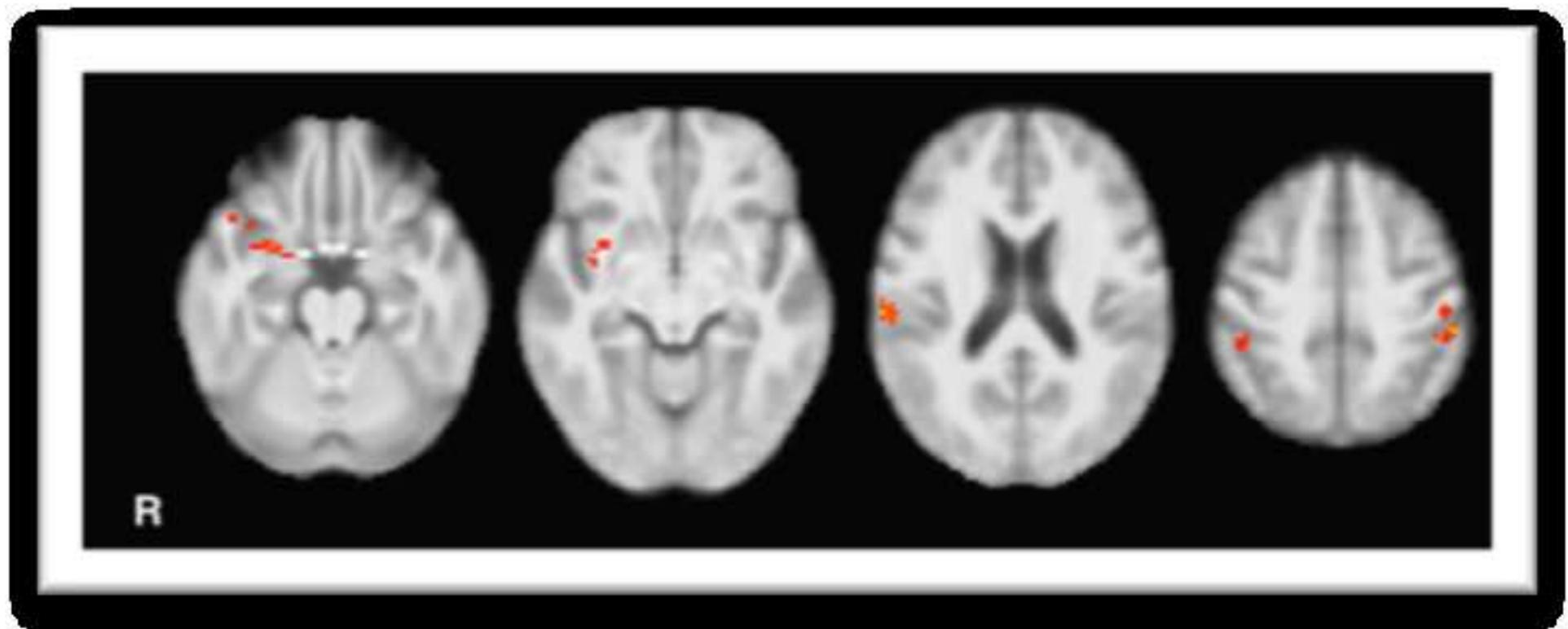
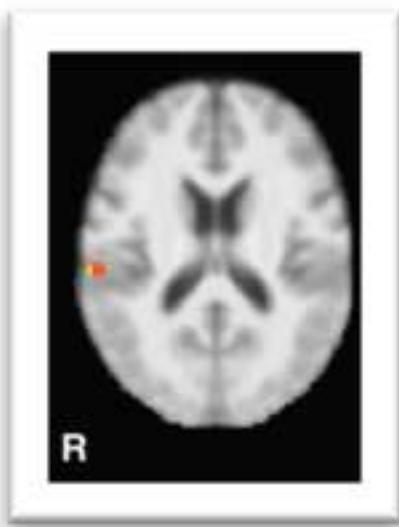
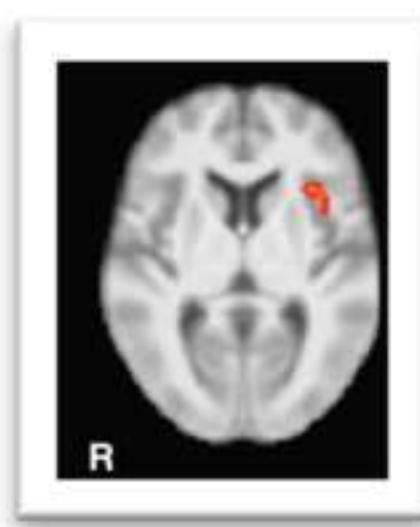


Figure 5

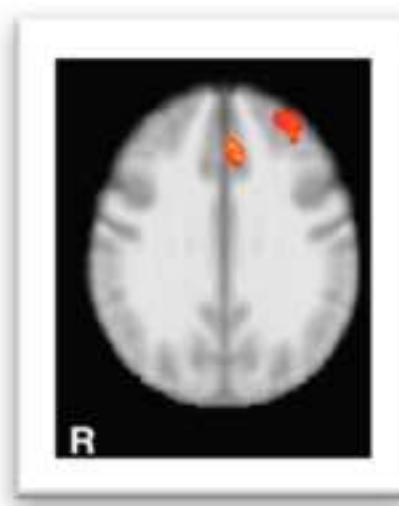
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A

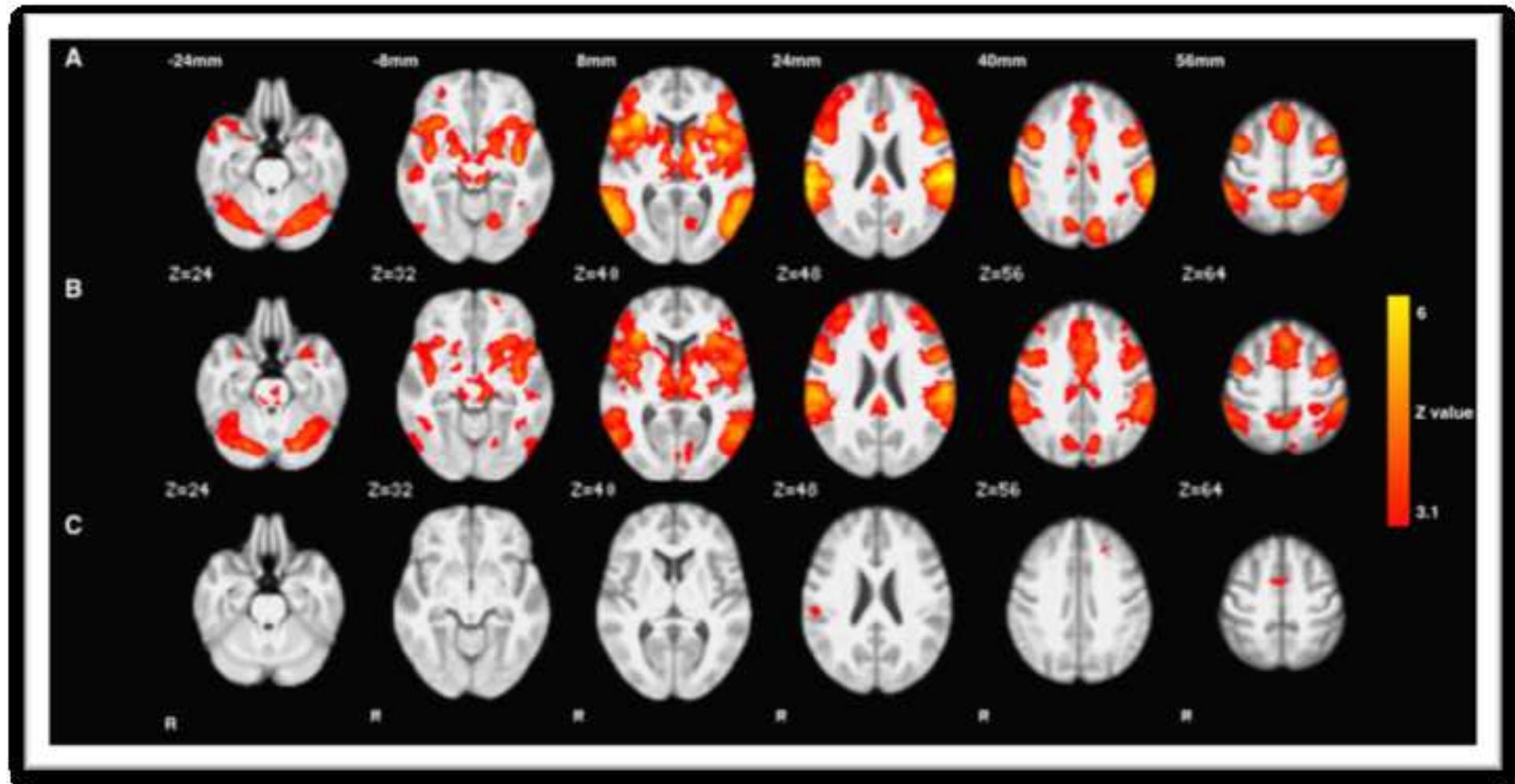


B

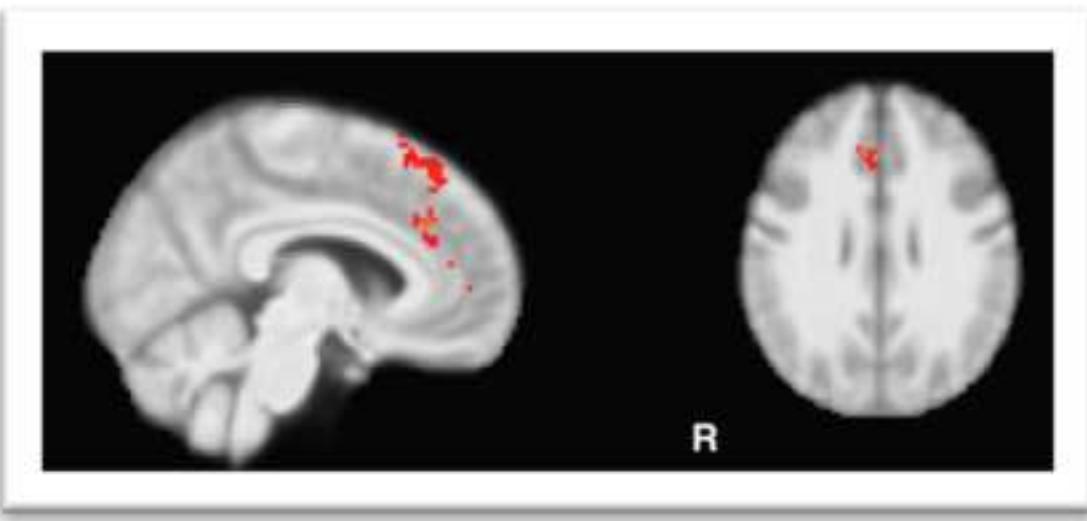
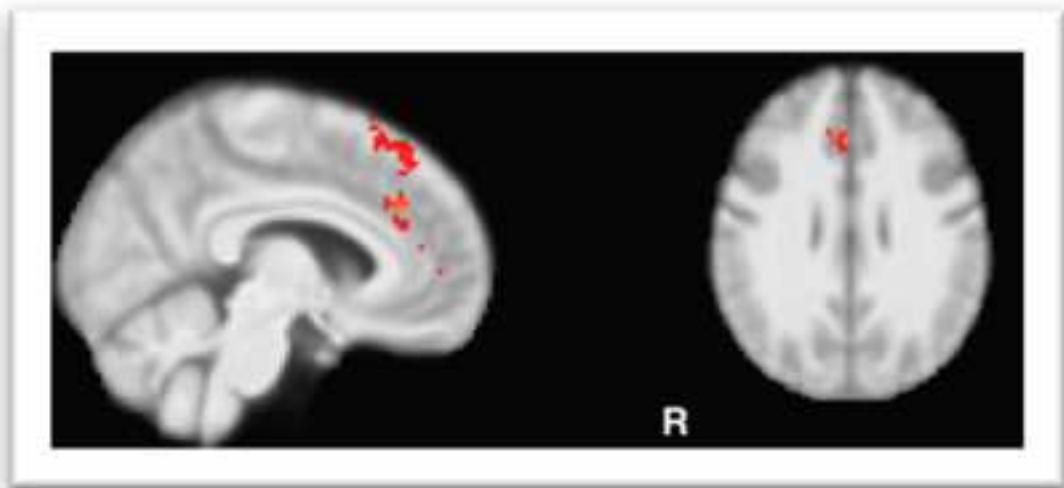
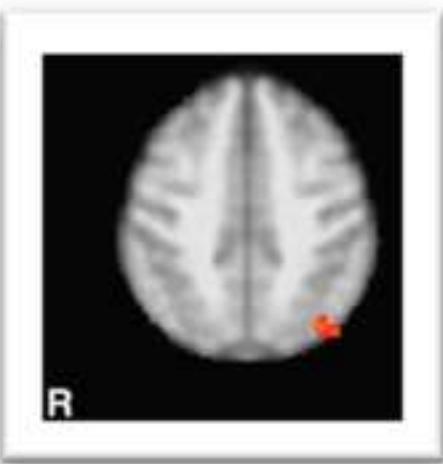


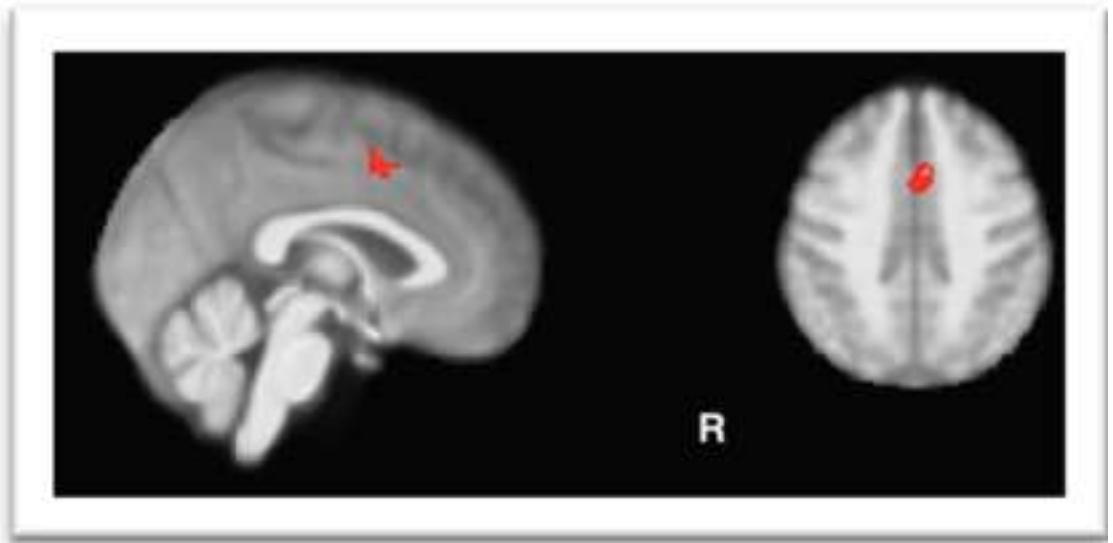
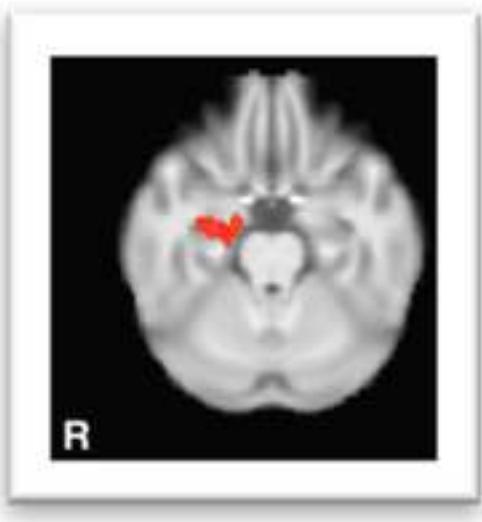
C

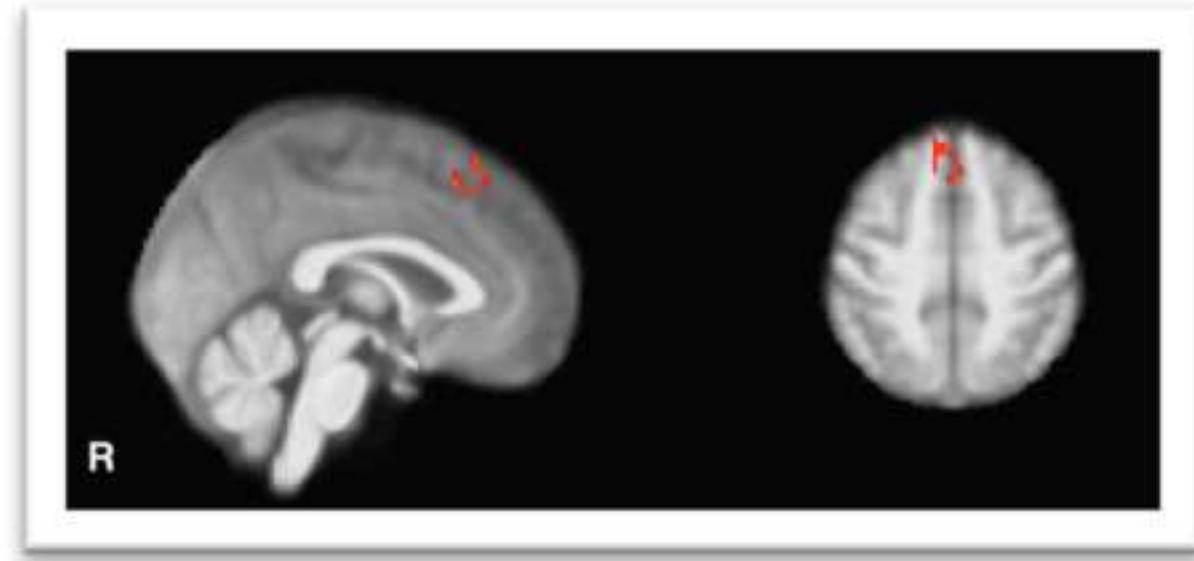
Figure 6

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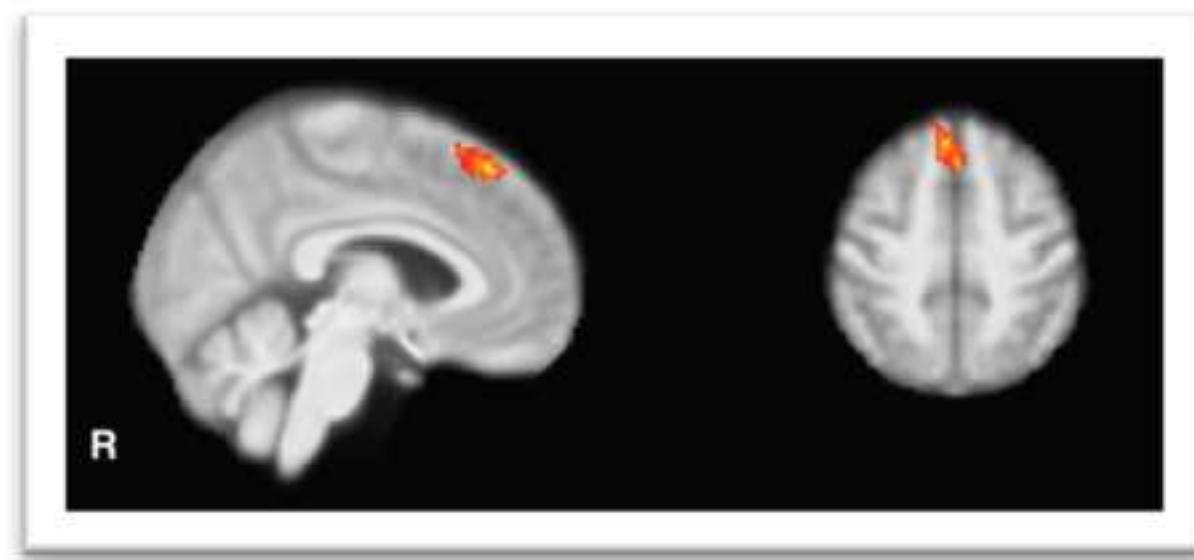




**A.****B.****C.**



A. F-test



B. $\text{AO}(\text{bl}>\text{fu}) > \text{ASAD}(\text{bl}>\text{fu})$

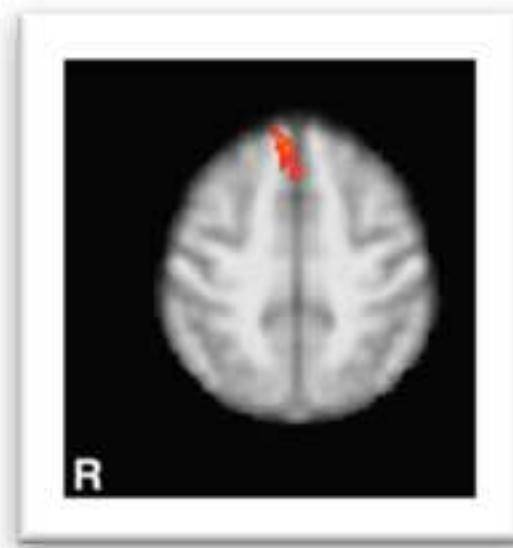
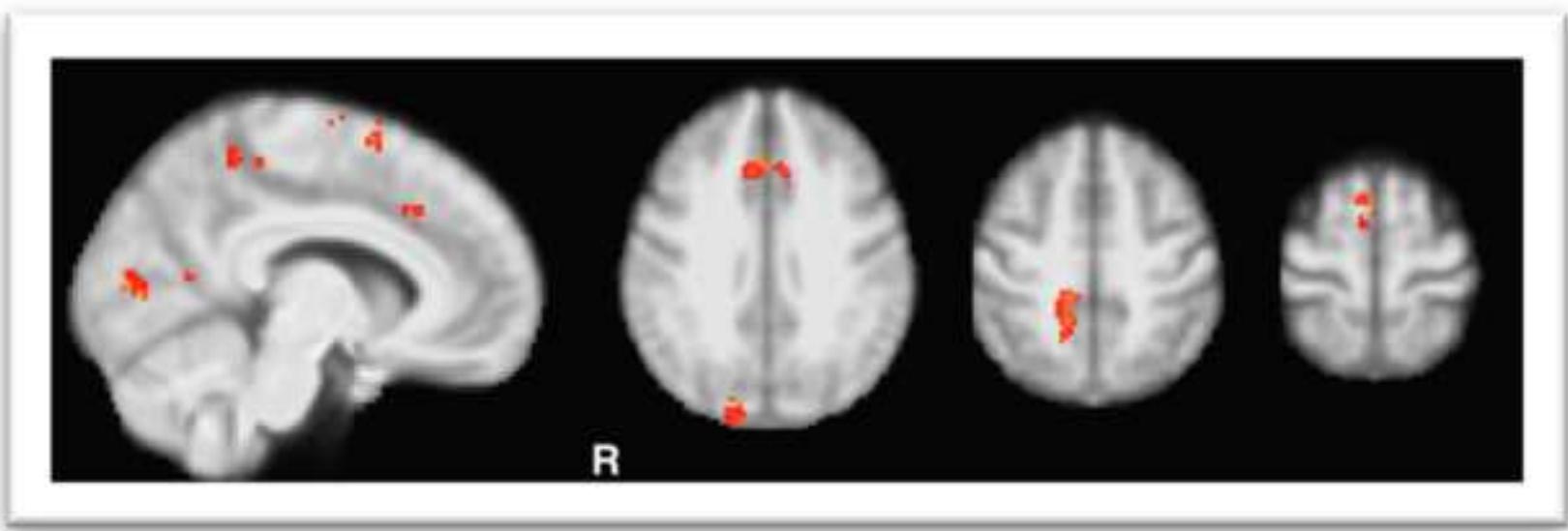
**A.****B.****C.**

Table 1 – Demographics and clinical characteristics

Baseline characteristics	All patients N=67	ASAD N=22	AO N=24	AMSR N=21	Between-groups comparison (ANOVA/ Fisher's exact test)
Age in years, Mean ± SD	51.4 ± 11.5	51.5 ± 10.4	52.4 ± 12.8	50.1 ± 11.4	F(df2)=0.22, p=0.81
Female, N (%)	25 (37%)	7 (32%)	12 (50%)	6 (29%)	chi2(df2) = 59.81, p=0.5
Right shoulder affected, N (%)	46 (69%)	13 (59%)	16 (67%)	17 (81%)	chi2(df2) = 2.5, p=0.31
Symptoms duration in months, Median (IQR*)	24 (18-36)	24 (18-36)	24 (18-36)	26 (14-48)	F(df2) = 0.24, p=0.89 *
Oxford Shoulder Score (OSS), Mean ± SD	27.3 ± 7.5	26.0 ± 6.8	29.1 ± 7.7	26.7 ± 8.0	F(df2) = 1.08, p=0.35
Present Pain Intensity (PPI), Mean ± SD	2.9 ± 2.4	2.4 ± 2.2	3.6 ± 2.5	2.7 ± 2.4	F(df2) = 1.8, p=0.17
PainDETECT (PD-Q), Mean ± SD	10.9 ± 6.0	12.2 ± 6.3	10.1 ± 6.0	10.5 ± 5.9	F(df2) = 0.79, p=0.46
PD-Q ≤ 12 , N (%)	44 (66%)	11/22 (50%)	19/24 (79%)	14/21 (67%)	chi2(df2)=4.34, p=0.12
PD-Q 12- 19, N (%)	10 (15%)	7/22 (32%)	1/24 (4%)	4/21 (19%)	chi2(df2)=4.10, p=0.14
PD-Q ≥ 19, N (%)	13 (19%)	4/22 (18%)	3/24 (13%)	3/21 (14%)	chi2(df2)=0.30, p=0.91
HADS total score, Mean ± SD	11.7 ± 7.5	12.6 ± 7.4	11.1 ± 6.7	11.4 ± 8.6	F(df2) = 0.25, p=0.78
Anxiety subscale, Mean ± SD	6.7 ± 4.4	7.1 ± 4.2	6.7 ± 4.3	6.3 ± 4.7	F(df2) = 0.26, p=0.88
Depression subscale, Mean ± SD	5.0 ± 4.0	4.4 ± 3.1	5.5 ± 4.0	5.5 ± 4.0	F(df2) = 0.46, p=0.63
Expectations:					chi2(df2) = 4.93, p=0.57
very much improved	25 (38%)	6 (27%)	12 (50%)	7 (33%)	
much improved	17 (26%)	7 (32%)	4 (17%)	6 (29%)	
minimally improved	23 (35%)	8 (36%)	7 (29%)	8 (38%)	
no change	1 (2%)	0 (0%)	1 (4%)	0 (0%)	
von Frey sharpness, Mean ± SD	2.5 ± 2.5	2.4 ± 2.5	2.0 ± 2.4	3.5 ± 2.4	F(df2)=2.27, p=0.11
von Frey pain, Mean ± SD	0.5 ± 1.5	0.98 ± 2.2	0.38 ± 1.1	0.06 ± 0.2	F(df2)=1.99, p=0.15
von Frey ongoing, Mean ± SD	2.3 ± 2.6	2.1 ± 2.3	2.2 ± 2.4	2.6 ± 3.2	F(df2)=0.22, p=0.80
Pain-killers on the day, N (%)	20 (30%)	6/22 (27%)	7/24 (29%)	7/21 (33%)	chi2(df2)=0.20, p=0.95
Radiating pain, N (%)	54 (81%)	17/22 (77%)	19/24 (79%)	18/21 (86%)	chi2(df2)=0.54, p=0.80
Abnormal sensation, N (%)	32 (48%)	11/22 (50%)	8/24 (33%)	13/21 (62%)	chi2(df2)=3.73, p=0.16
Other pain, N (%)	30 (45%)	15/22 (68%)	12/24 (50%)	11/21 (52%)	chi2(df2)=1.78, p=0.44

* - Interquartile Range

& - Kruskal-Wallis (non-parametric equivalent of ANOVA)

Table 2 – Within-arm changes in clinical and psychological measures

Intention-to-treat	Baseline	Baseline (pair)	Follow-up	Difference	Paired t-test p
ASAD					
OSS	26.0 ± 6.8 (N=22)	27.0 ± 6.7	35.6 ± 9.7	8.6 ± 10.4 (N=18)	0.003
PPI	2.4 ± 2.3 (N=22)	2.3 ± 2.1	1.1 ± 2.0	-1.2 ± 2.6 (N=18)	0.07
PD-Q	12.2 ± 6.3 (N=22)	11.3 ± 5.9	7.9 ± 5.6	-3.4 ± 5.3 (N=18)	0.02
HADS	12.6 ± 7.4 (N=22)	11.8 ± 7.6	8.7 ± 10.5	-3.2 ± 6.9 (N=18)	0.07
MDT affected	-1.3 ± 1.7 (N=20)	-0.9 ± 1.6	-0.8 ± 1.7	0.04 ± 1.7 (N=16)	0.92
MDT contralateral	-1.3 ± 1.6 (N=20)	-1.1 ± 1.6	0.84 ± 1.5	0.2 ± 0.83 (N=16)	0.27
MPT affected	0.1 ± 1.7 (N=21)	0.03 ± 1.4	0.6 ± 1.2	0.6 ± 1.6 (N=16)	0.17
MPT contralateral	0.5 ± 1.3 (N=21)	0.4 ± 1.4	0.7 ± 0.9	0.3 ± 1.5 (N=16)	0.46
PPT affected	1.4 ± 1.1 (N=21)	1.3 ± 0.8	0.7 ± 1.2	-0.6 ± 1.3 (N=15)	0.12
PPT contralateral	1.1 ± 1.1 (N=21)	1.1 ± 0.9	0.8 ± 1.1	-0.4 ± 0.9 (N=15)	0.15
PPT sternum	1.4 ± 1.2 (N=21)	1.2 ± 1.1	0.8 ± 1.0	-0.4 ± 0.9 (N=15)	0.07
von Frey ongoing	2.2 ± 2.5 (N=21)	2.1 ± 2.5	3.6 ± 2.7	1.6 ± 2.8 (N=17)	0.04
von Frey sharpness	2.1 ± 2.3 (N=21)	2.1 ± 2.1	1.3 ± 2.4	-0.9 ± 2.7 (N=17)	0.19

Intention-to-treat AO	Baseline	Baseline (pair)	Follow-up	Difference	Paired t-test p
OSS	29.1 ± 7.7 (N=24)	30.1 ± 7.0	36.0 ± 6.04	5.9 ± 8.8 (N=21)	0.006
PPI	3.6 ± 2.5 (N=24)	4.1 ± 2.3	1.6 ± 2.2	-2.5 ± 2.1 (N=21)	0.0000
PD-Q	10.1 ± 6.0 (N=24)	9.9 ± 6.2	6.3 ± 3.9	-3.6 ± 6.4 (N=21)	0.02

<i>HADS</i>	11.1 ± 6.7 (N=24)	10.6 ± 6.9	9.0 ± 5.6	-1.6 ± 4.4 (N=21)	0.11
<i>MDT affected</i>	-0.8 ± 1.9 (N=24)	-0.8 ± 1.8	-1.1 ± 1.8	-0.3 ± 1.2 (N=21)	0.21
<i>MDT contralateral</i>	-0.7 ± 1.5 (N=24)	-0.7 ± 1.5	-1.2 ± 1.6	-0.4 ± 1.6 (N=21)	0.23
<i>MPT affected</i>	-0.4 ± 1.1 (N=24)	-0.3 ± 1.1	-0.008 ± 1.3	0.3 ± 1.4 (N=21)	0.34
<i>MPT contralateral</i>	-0.2 ± 1.3 (N=24)	-0.2 ± 1.3	-0.1 ± 1.3	0.05 ± 1.3 (N=21)	0.86
<i>PPT affected</i>	0.6 ± 1.0 (N=16)	0.6 ± 1.1	0.3 ± 1.0	-0.3 ± 1.2 (N=12)	0.39
<i>PPT contralateral</i>	0.8 ± 1.0 (N=17)	0.9 ± 1.0	0.5 ± 0.9	-0.5 ± 1.1 (N=13)	0.16
<i>PPT sternum</i>	0.6 ± 0.9 (N=17)	0.7 ± 0.94	0.6 ± 0.8	-0.1 ± 0.8 (N=13)	0.64
<i>von Frey ongoing</i>	2.0 ± 2.4 (N=24)	2.3 ± 2.4	2.8 ± 1.8	0.5 ± 2.8 (N=21)	0.39
<i>von Frey sharpness</i>	2.2 ± 2.4 (N=23)	2.4 ± 2.5	1.8 ± 2.4	-0.6 ± 2.3 (N=21)	0.22

<i>Intention-to-treat</i>	<i>Baseline</i>	<i>Baseline</i>	<i>Follow-up</i>	<i>Difference</i>	<i>Paired t-test p</i>
<i>AMSR</i>	<i>(pair)</i>				
OSS	26.7 ± 8.0 (N=21)	26.3 ± 7.8	31.1 ± 11.5	4.8 ± 6.3 (N=16)	0.008
PPI	2.7 ± 2.4 (N=21)	2.8 ± 2.6	3.3 ± 3.6	0.5 ± 2.0 (N=16)	0.33
PD-Q	10.5 ± 5.9 (N=21)	10.1 ± 5.8	8.8 ± 6.5	-1.3 ± 5.2 (N=16)	0.35
HADS	11.4 ± 8.6 (N=21)	11.3 ± 9.1	11.8 ± 9.7	0.5 ± 4.8 (N=16)	0.68
<i>MDT affected</i>	-1.0 ± 1.7 (N=20)	-1.1 ± 1.6	-1.7 ± 1.9	-0.6 ± 1.4 (N=16)	0.12
<i>MDT contralateral</i>	-1.4 ± 1.9 (N=20)	-1.5 ± 1.8	-1.6 ± 1.8	-0.07 ± 1.2 (N=16)	0.83
<i>MPT affected</i>	0.5 ± 1.0 (N=21)	0.5 ± 1.1	0.4 ± 0.9	-0.08 ± 1.5 (N=16)	0.85
<i>MPT contralateral</i>	0.3 ± 1.0 (N=21)	0.5 ± 1.0	0.7 ± 0.8	0.2 ± 1.1 (N=16)	0.45
<i>PPT affected</i>	1.1 ± 1.4 (N=19)	0.9 ± 1.5	0.6 ± 1.2	-0.4 ± 1.4 (N=14)	0.34
<i>PPT contralateral</i>	0.7 ± 1.1 (N=19)	0.5 ± 1.1	0.5 ± 1.1	0.06 ± 1.3 (N=14)	0.87
<i>PPT sternum</i>	1.2 ± 1.0 (N=19)	1.1 ± 1.1	0.6 ± 1.1	-0.4 ± 1.0 (N=14)	0.14
<i>von Frey ongoing</i>	2.6 ± 3.2 (N=19)	2.4 ± 3.1	2.3 ± 3.3	-0.03 ± 1.8 (N=16)	0.95
<i>von Frey sharpness</i>	3.5 ± 2.4 (N=18)	3.2 ± 2.3	3.7 ± 2.5	0.5 ± 4.0 (N=15)	0.61

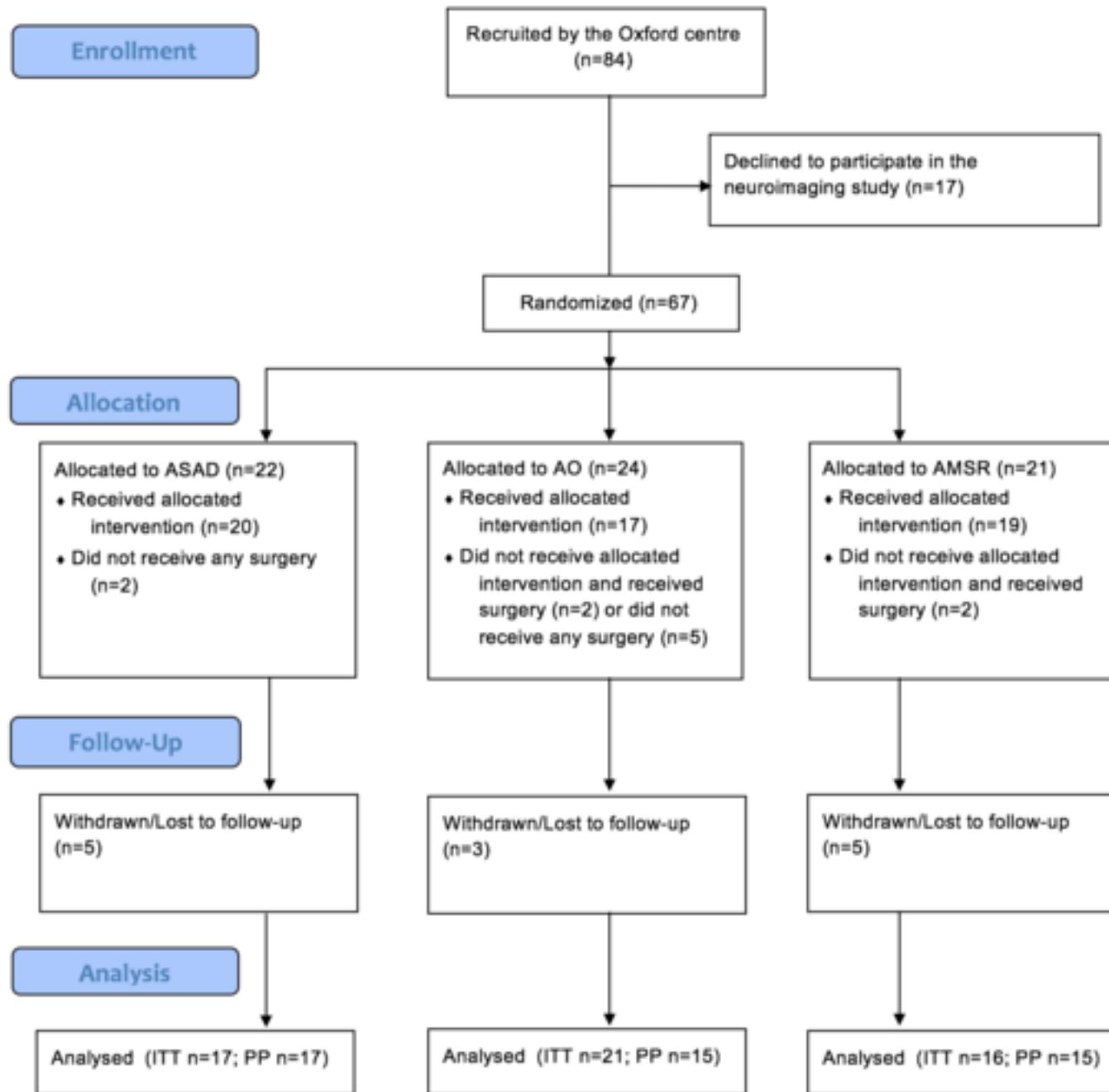
The QST values are analysed as reversed Z-scores. No age and sex in the regression model.

Table 3 - Between-arm changes in clinical and psychophysical measures

<i>ITT</i>	<i>ASAD vs AO</i>		<i>ASAD vs AMSR</i>	
	<i>Outcomes</i>	<i>MD (95% CI) [p-value]</i>	<i>MD (95% CI) [p-</i>	<i>MD (95% CI) [p-value]</i>
OSS	0.92 (-4.78, 6.61)	4.05 (-1.76, 9.86)	3.13 (-2.75, 9.02)	
PPI	0.92 (-0.60, 2.44)	-1.82 (-3.29, -0.34)	-2.74 (-4.26, -1.22)	
PD-Q	0.16 (-2.8, 3.1)	-1.73 (-4.79, 1.33)	-1.46 (-5.25, 0.84)	
HADS	-1.2 (-4.88, 2.48)	-3.65 (-7.45, 0.15)	-2.45 (-6.24, 1.34)	
<i>MDT affected</i>	-0.1 (-0.38, 0.18)	-0.22 (-0.51, 0.070)	-0.12 (-0.40, 0.16)	
<i>MDT contralateral</i>	-0.14 (-0.39, 0.11)	-0.16 (-0.42, 0.10)	-0.017 (-0.27, 0.24)	

<i>MPT affected</i>	-0.17 (-0.44, 0.11)	-0.054 (-0.33, 0.22)	0.090 (-0.19, 0.36)
<i>MPT contralateral</i>	-0.19 (-0.43, 0.05]	0.020 (-0.23, 0.27)	0.21 (-0.032, 0.46)
<i>PPT affected</i>	-0.67 (-0.21, 0.08)	-0.023 (-0.15, 0.11)	0.044 (-0.10, 0.19)
<i>PPT contralateral</i>	-0.05 (-0.16, 0.07)	0.0079 (-0.11, 0.12)	0.053 (-0.067, 0.17)
<i>PPT sternum</i>	0.029 (-0.079, 0.14;)	-0.009 (-0.11, 0.09)	-0.038 (-0.15, 0.07)
<i>von Frey ongoing</i>	-0.19 (-1.65, 1.27)	-0.93 (-2.43, 0.58)	-0.74 (-2.22, 0.74)
<i>von Frey sharpness</i>	0.64 (-0.96, 2.24)	0.039 (-1.67, 1.75)	-0.60 (-2.27, 1.08)

The QST values are log-transformed. Age and sex in the model



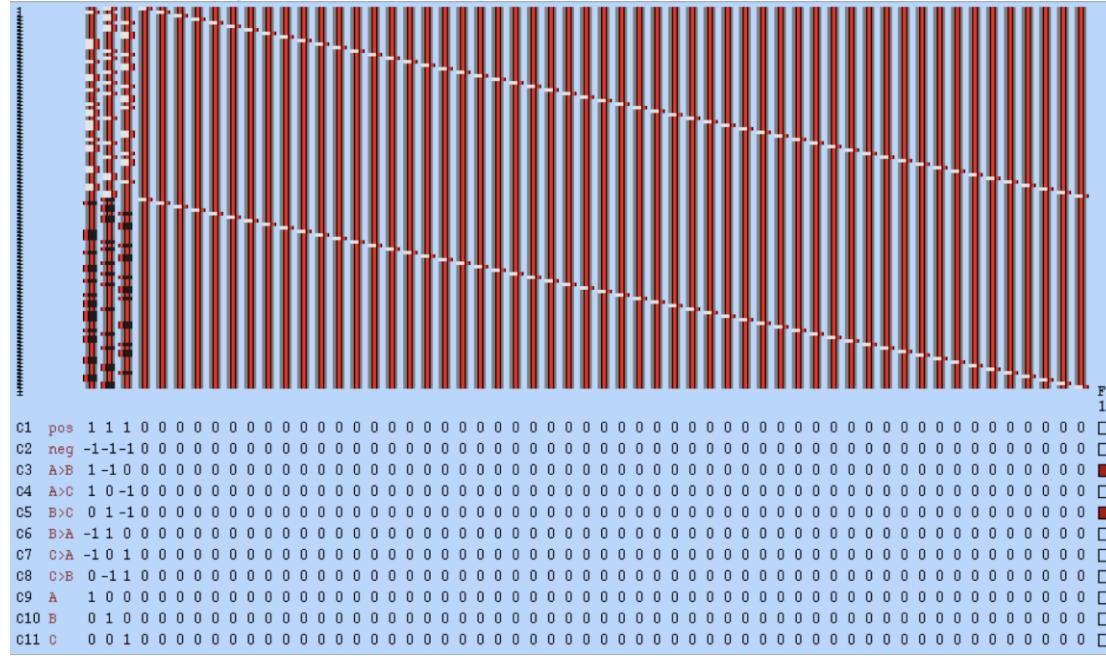


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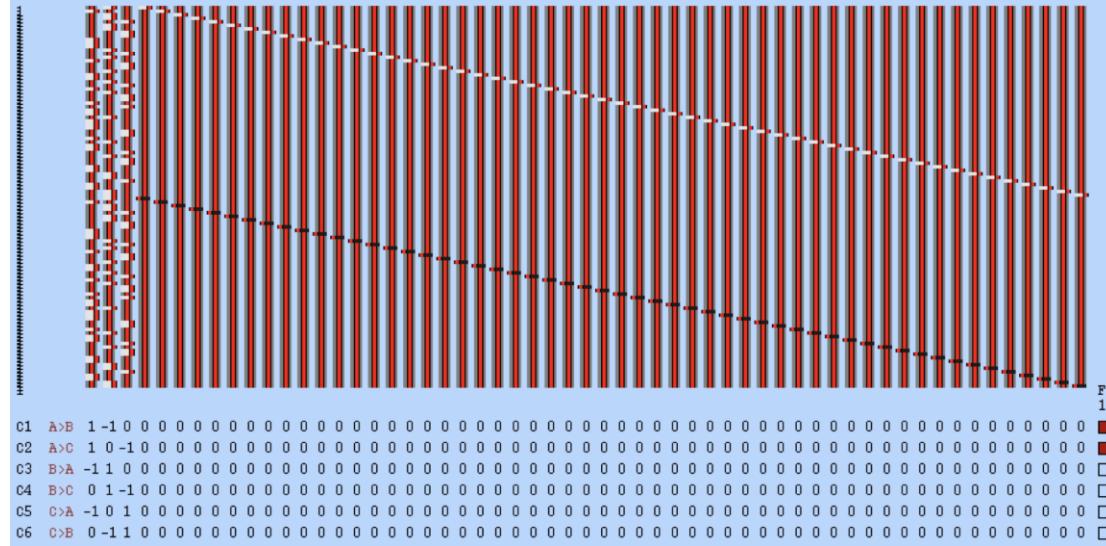
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Treatment effect analysis models

2-level model - design 1- within-arm differences

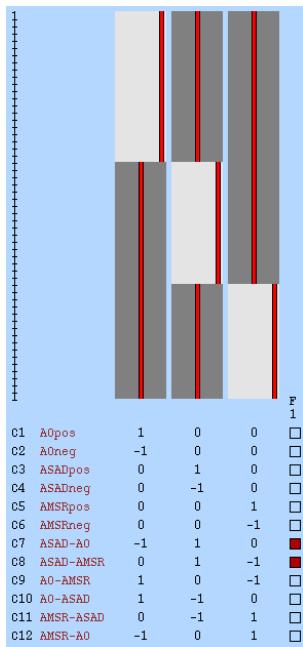


2-level model - design 2- between-arm differences



3-level model (sensitivity analysis)

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QST Profiles

We have also converted the log-transformed QST values into Z scores as recommended by the DFNS and as has been reported in the literature. [we used both, the log-transformed QST scores and Z-scores because of their respective strengths and weaknesses – raw values represent a continuous variable corresponding to the actual measurements, without relative cut-offs but which depends on age and sex; Z-scores – represent difference from control mean controlling for age and sex but depend on the normative dataset and are usually interpreted as within and beyond Z of +/-1.96. As there are no normative data for the shoulder region, we used controls' data as the normative data; separately for older and younger patients (median split at 50 years) and for men and women.[58][59] because both age and gender affect QST values. [7][41][58][48] Averaged control data were used for Z-score calculations (like in [58][25]) as there were no differences between the left and right shoulder. (N.B. the assessment order had no effect.). The sign of Z-score was reversed so that values over 1.96 indicated gain of function (patients more sensitive than controls) and values below -1.96 indicated loss of function.[49] We also calculated the frequency of values over and below the normal range.[49]

In the control group, there were no significant differences between left and right side and no effect of the order of assessment (left or right assessed first) so the averaged left-right values were used as the reference data (as in Curatolo et al. [58]). There was an effect of sex had effect on all three (MDT, MPT, PPT) but age had effect only on MPT.

Supplementary Table 1 – Normative values – raw data

	Gender	Age	Mean	LCI	UCI	10 th percentile	90 th percentile
MDT	Female	<50	0.09	0.06	0.13	0.04	0.18
	Female	≥ 50	0.12	0.09	0.14	0.07	0.20

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	Male	<50	0.21	0.17	0.28	0.08	0.49
	Male	≥ 50	0.17	0.11	0.26	0.07	0.31
MPT	Female	<50	28.84	19.95	41.69	12.59	60.13
	Female	≥ 50	45.71	32.36	66.07	21.88	140.07
	Male	<50	51.29	38.90	69.18	14.79	118.60
	Male	≥ 50	100.00	67.61	151.36	50.12	249.04
PPT	Female	<50	23.99	20.89	28.18	15.49	30.72
	Female	≥ 50	26.30	20.42	34.67	13.18	70.0
	Male	<50	44.67	39.81	50.12	26.92	70.0
	Male	≥ 50	43.65	51.29	51.29	27.54	60.04

Supplementary Table 2 – Normative values – log-transformed data

	Gender	Age	Mean	LCI	UCI	10 th percentile	90 th percentile
logMDT	Female	<50	-1.05	-1.22	-0.89	-1.41	-0.74
	Female	≥ 50	-0.93	-1.03	-0.84	-1.16	-0.69
	Male	<50	-0.67	-0.77	-0.56	-1.12	-0.31
	Male	≥ 50	-0.76	-0.94	-0.58	-1.13	-0.51
logMPT	Female	<50	1.46	1.30	1.62	1.10	1.78
	Female	≥ 50	1.66	1.51	1.82	1.34	2.15
	Male	<50	1.71	1.59	1.84	1.17	2.07
	Male	≥ 50	2.00	1.83	2.18	1.70	2.40
logPPT	Female	<50	1.38	1.32	1.45	1.19	1.49
	Female	≥ 50	1.42	1.31	1.54	1.12	1.85
	Male	<50	1.65	1.60	1.70	1.43	1.85
	Male	≥ 50	1.64	1.71	1.71	1.44	1.79

Frequency of abnormal QST values

Frequency distribution of sensory abnormalities classified as gain, normal and loss of sensory function for each QST parameters

Supplementary Table 3- Frequency of abnormal QST values (patient group at baseline)

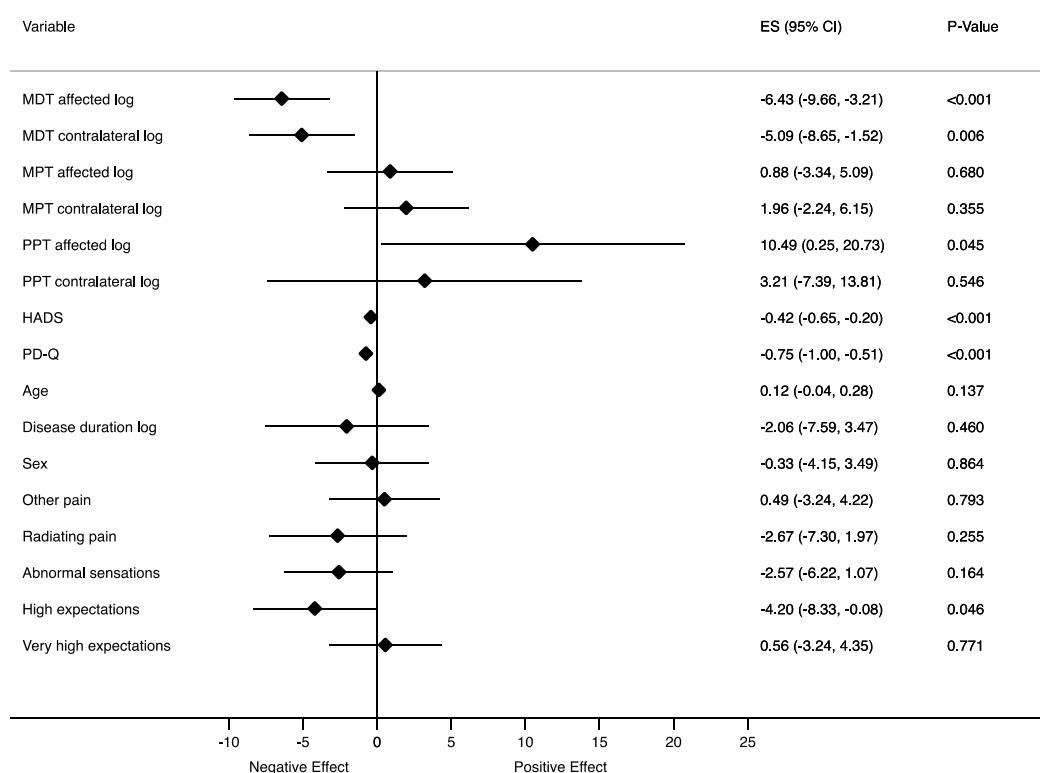
QST parameter	Loss of function (Hypoesthesia) ≤-1.96	Normal range -1.96 to 1.96	Gain of function (Hyperesthesia) ≥1.96	
			Affected arm	Contralateral arm
Mechanical Detection Threshold (MDT)				
Affected arm	17/64 (27%)	44/64 (69%)	3/64 (5%)	
Contralateral arm	16/64 (25%)	48/64 (75%)	0/64 (0%)	
Mechanical Pain Threshold (MPT)				
Affected arm	5/66 (8%)	57/66 (86%)	4/66 (6%)	
Contralateral arm	4/66 (6%)	56/66 (86%)	6/66 (9%)	
Pressure Pain Threshold (PPT)				
Affected arm	0/56 (0%)	43/56 (77%)	13/56 (23%)	
Contralateral arm	0/57 (0%)	47/57 (82%)	10/57 (18%)	
Sternum	0/57 (0%)	41/57 (72%)	16/57 (28%)	

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Supplementary Table 4 – Frequency of abnormal QST values – by trial arm

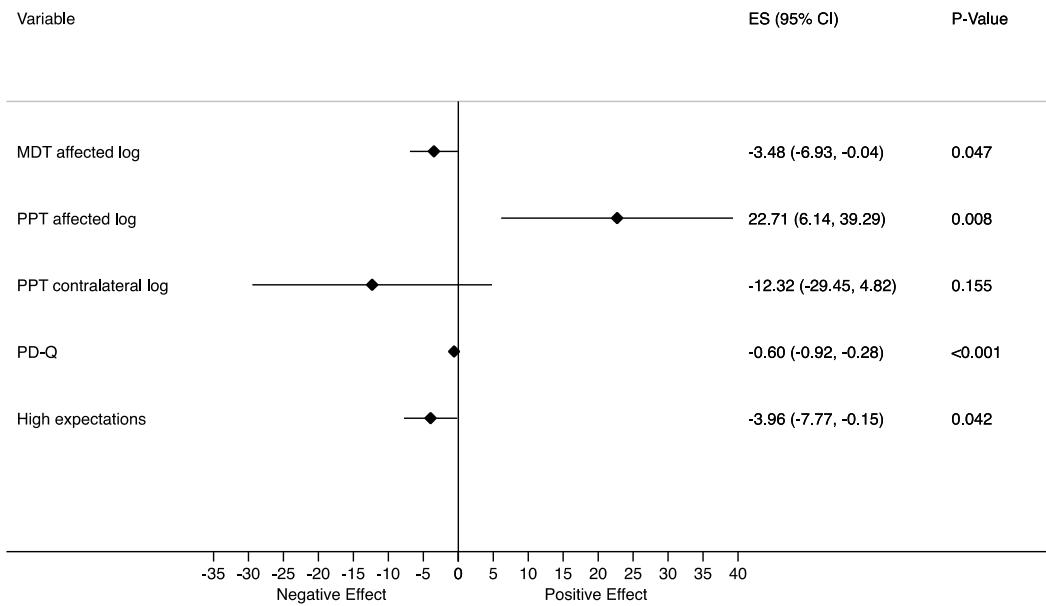
	ASAD	AO	AMSR	P value
MDT hypoesthesia affected side	7/20	6/24	4/20	Chi2(df2)=1.2 p=0.53
MDT hypoesthesia contralateral side	5/20	4/24	7/20	Chi2(df2)=1.96 p=0.37
PPT hyperalgesia affected side	5/21	2/16	6/19	Chi2(df2)=1.78 p=0.45
PPT hyperalgesia contralateral side	5/21	3/17	2/19	Chi2(df2)=1.22 p=0.57

Explanatory value of QST and expectations

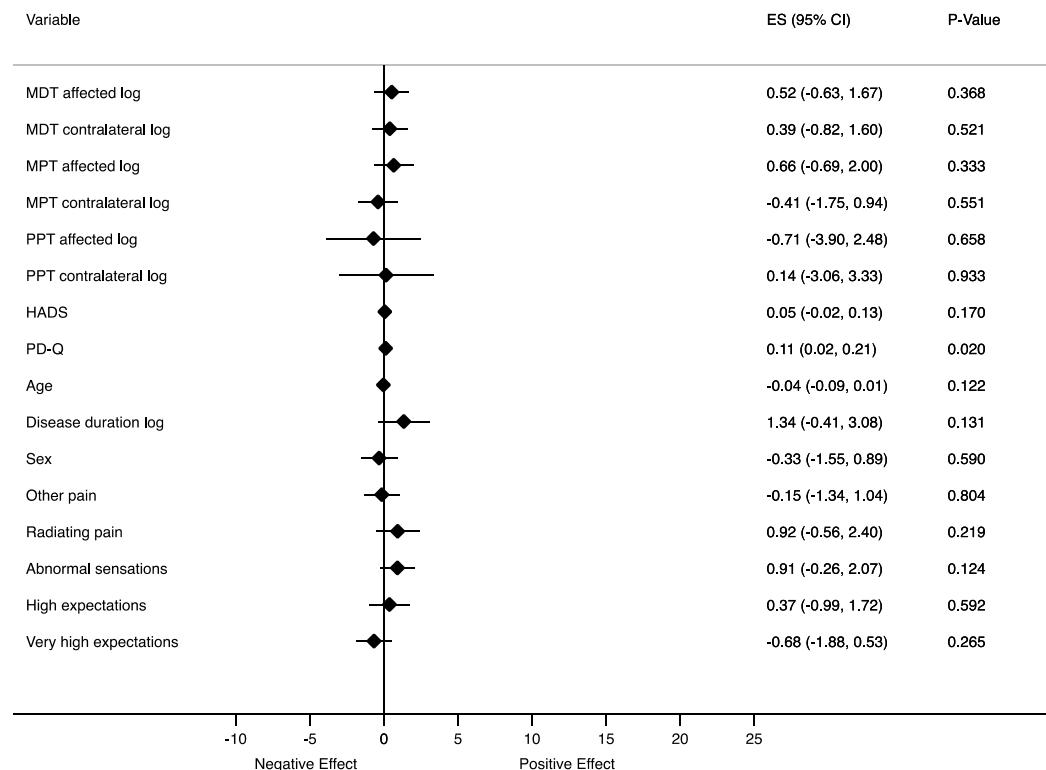


Supplementary Figure 1 – OSS univariate analysis

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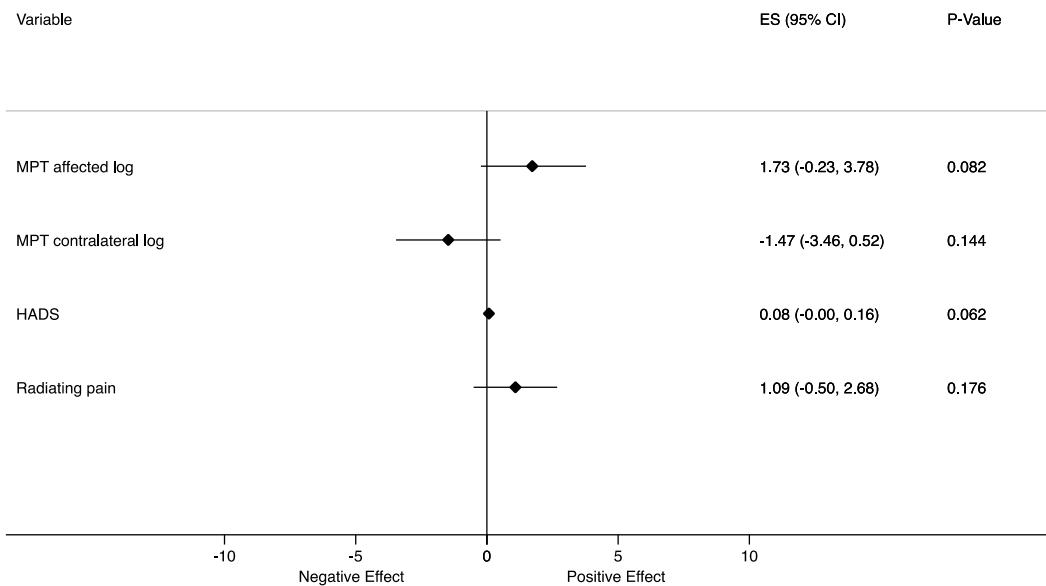


Supplementary Figure 2 – OSS multivariate analysis

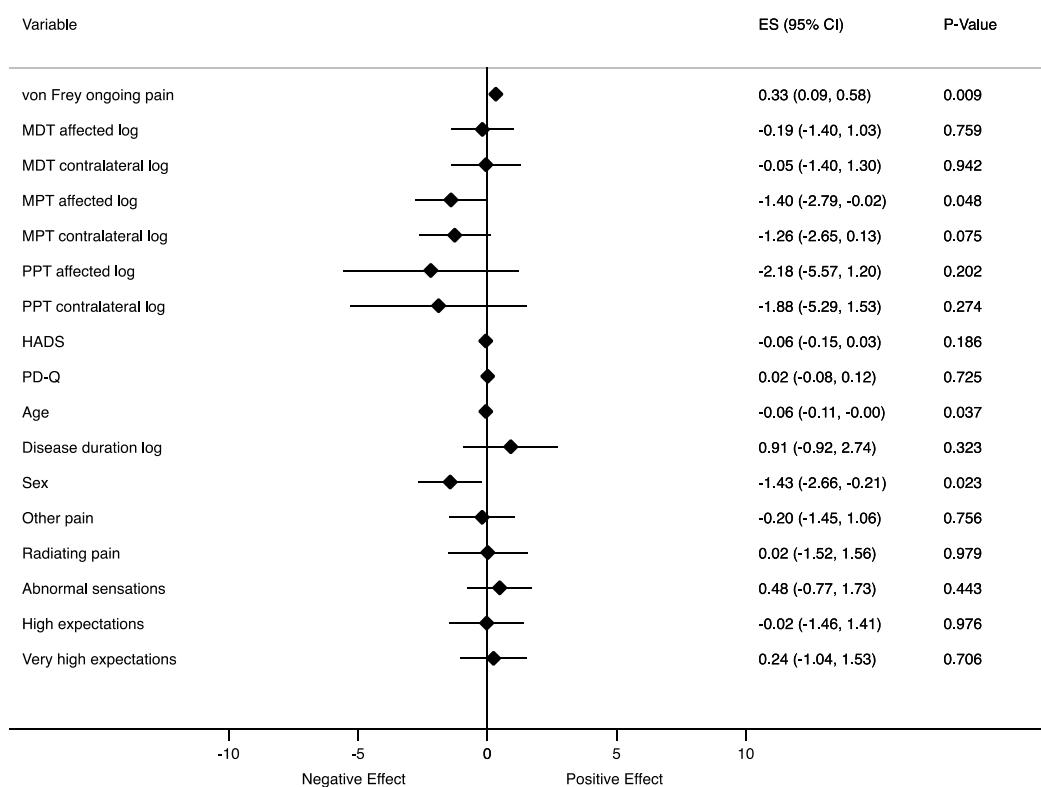


Supplementary Figure 3 – PPI univariate analysis

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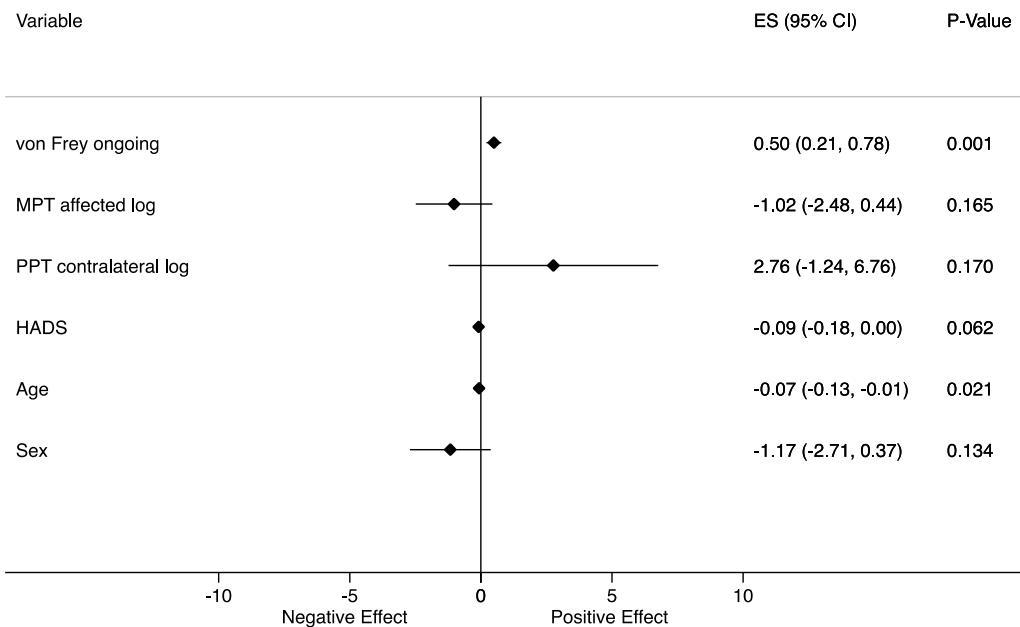


Supplementary Figure 4 - PPI multivariate analysis

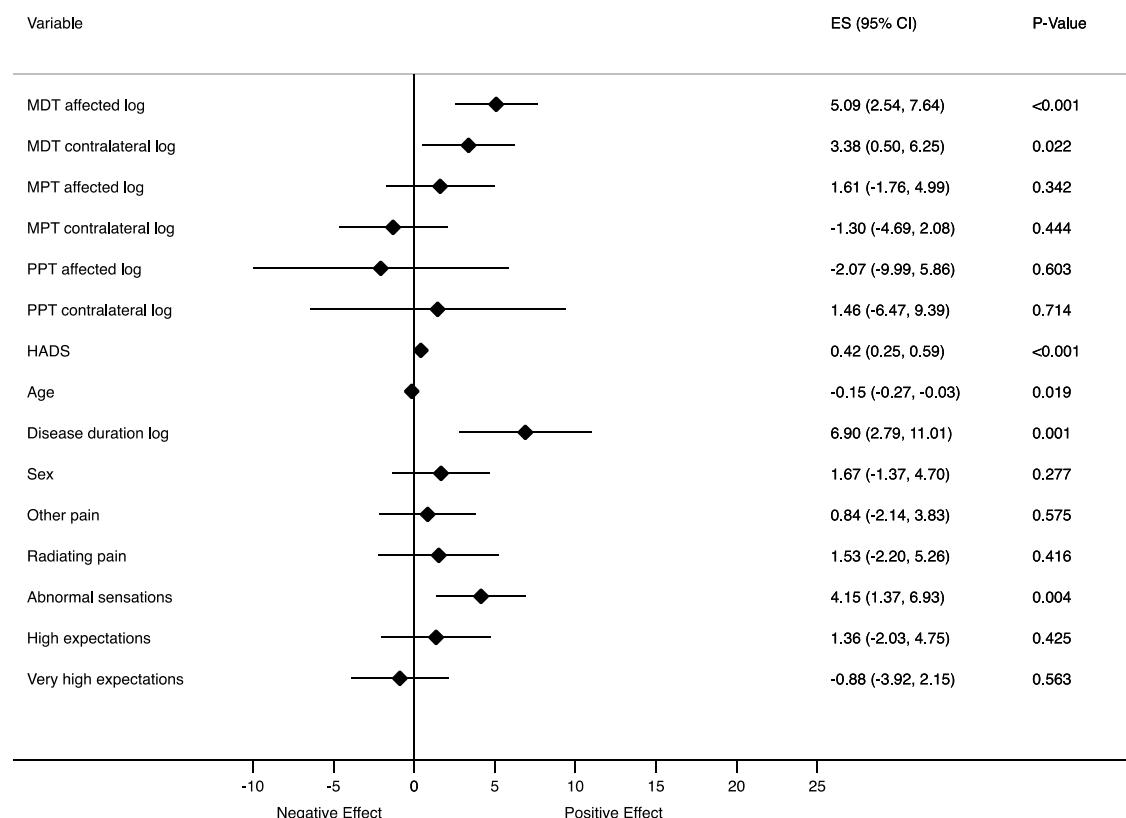


Supplementary Figure 5 - von Frey sharpness ratings univariate analysis

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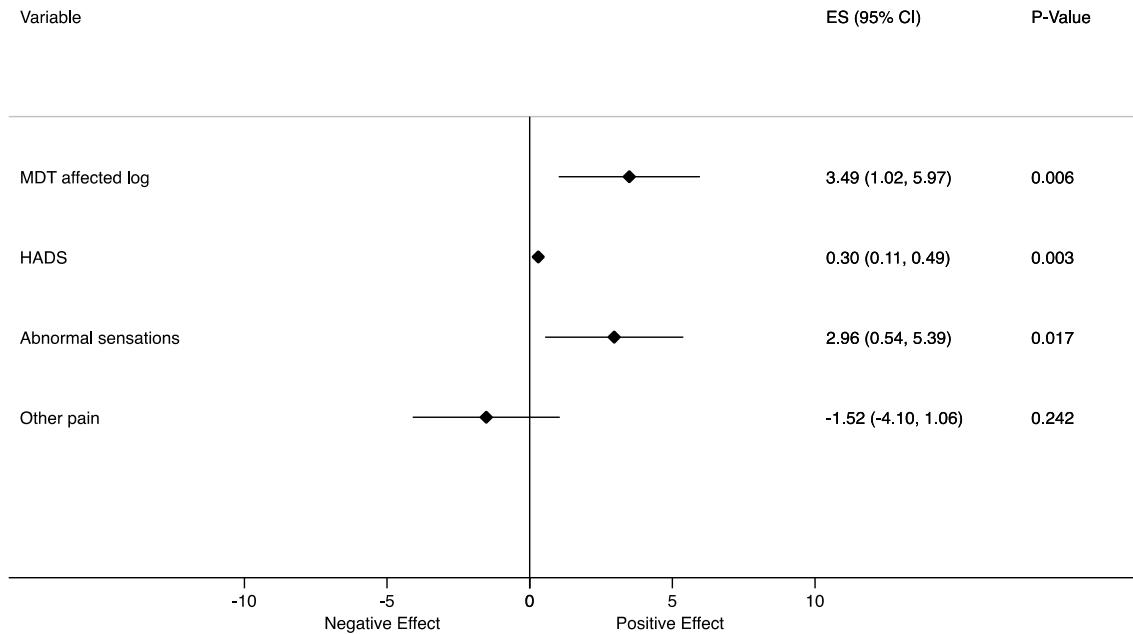


Supplementary Figure 6 - von Frey sharpness ratings multivariate analysis



Supplementary Figure 7 – PD-Q univariate analysis

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Supplementary Figure 8 – PD-Q multivariate analysis

Treatment effect – per-protocol analysis

Supplementary Table 5 - Within-arm changes in clinical and psychophysical measures - per-protocol analysis

Per protocol ASAD	Baseline (pair)	Follow-up	Difference fu>bl	Paired t-test p
OSS	27.0 ± 6.7	35.6 ± 9.7	-8.6 ± 10.4 (N=18)	0.003
PPI	2.3 ± 2.1	1.1 ± 2.0	-1.2 ± 2.6 (N=18)	0.07
PD-Q	11.3 ± 5.9	7.9 ± 5.6	-3.4 ± 5.3 (N=18)	0.02
HADS	11.8 ± 7.6	8.7 ± 10.5	-3.2 ± 6.9 (N=18)	0.07
MDT affected	-0.9 ± 1.6	-0.8 ± 1.7	0.04 ± 1.7 (N=16)	0.92
MDT contralateral	-1.1 ± 1.6	-0.8 ± 1.5	0.2 ± 0.8 (N=16)	0.27
MPT affected	0.03 ± 1.4	0.6 ± 1.2	0.6 ± 1.6 (N=16)	0.17
MPT contralateral	0.4 ± 1.4	0.7 ± 0.9	0.3 ± 1.5 (N=16)	0.46
PPT affected	1.3 ± 0.8	0.7 ± 1.2	-0.6 ± 1.3 (N=15)	0.12
PPT contralateral	1.1 ± 0.9	0.8 ± 1.1	-0.4 ± 0.9 (N=15)	0.15
PPT sternum	1.2 ± 1.1	0.8 ± 1.0	-0.4 ± 0.9 (N=15)	0.07
von Frey ongoing	2.1 ± 2.1	1.3 ± 2.4	-0.9 ± 2.7 (N=17)	0.19
von Frey sharpness	2.1 ± 2.4	3.7 ± 2.7	1.6 ± 2.8 (N=17)	0.04
Per protocol AO	Baseline	Follow-up	Difference fu>bl	Paired t-test p
OSS	30.0 ± 7.5	36.1 ± 5.9	6.1 ± 8.7 (N=14)	0.02
PPI	5.0 ± 2.0	1.7 ± 2.4	-3.3 ± 1.9 (N=14)	<0.00005
PD-Q	11.0 ± 7.2	6.5 ± 4.3	-4.5 ± 7.2 (N=14)	0.04
HADS	12.1 ± 7.2	9.4 ± 6.3	-2.7 ± 4.6 (N=14)	0.05
MDT affected	-1.0 ± 1.9	-1.1 ± 1.5	-0.2 ± 0.9 (N=14)	0.47
MDT contralateral	-0.7 ± 1.7	-1.1 ± 1.1	-0.3 ± 1.6 (N=14)	0.43

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MPT affected	-0.3 ± 1.3	-0.3 ± 1.2	0.1 ± 1.4 (N=14)	0.84
MPT contralateral	-0.1 ± 1.3	-0.2 ± 1.1	-0.1 ± 1.3 (N=14)	0.80
PPT affected	0.02 ± 0.6	0.3 ± 0.8	0.3 ± 0.7 (N=8)	0.25
PPT contralateral	0.6 ± 1.0	0.7 ± 0.9	0.01 ± 0.5 (N=9)	0.94
PPT sternum	0.5 ± 0.9	0.7 ± 0.8	0.2 ± 0.7 (N=9)	0.46
von Frey ongoing	2.2 ± 2.3	1.6 ± 2.0	-0.5 ± 1.5 (N=14)	0.20
von Frey sharpness	2.9 ± 2.4	2.5 ± 1.8	-0.4 ± 2.2 (N=14)	0.54

Per protocol AMSR	Baseline (pair)	Follow-up	Difference fu>bl	Paired t-test p
OSS	25.8 ± 7.7	30.1 ± 11.1	-4.3 ± 6.2 (N=15)	0.018
PPI	2.9 ± 2.7	3.5 ± 3.6	0.6 ± 2.0 (N=15)	0.26
PD-Q	10.3 ± 6.0	8.9 ± 6.7	-1.3 ± 5.4 (N=15)	0.35
HADS	12.0 ± 9.0	12.5 ± 9.6	0.5 ± 5.0 (N=15)	0.69
MDT affected	-1.2 ± 1.6	-1.8 ± 1.9	-0.6 ± 1.4 (N=15)	0.13
MDT contralateral	-1.7 ± 1.8	-1.7 ± 1.8	-0.1 ± 1.3 (N=15)	0.85
MPT affected	0.5 ± 1.1	0.3 ± 0.8	-0.2 ± 1.6 (N=15)	0.71
MPT contralateral	0.5 ± 1.0	0.7 ± 0.8	0.2 ± 1.2 (N=15)	0.57
PPT affected	1.1 ± 1.5	0.6 ± 1.2	-0.4 ± 1.5 (N=13)	0.32
PPT contralateral	0.5 ± 1.1	0.6 ± 1.2	0.03 ± 1.4 (N=13)	0.94
PPT sternum	1.2 ± 1.0	0.7 ± 1.1	-0.5 ± 1.0 (N=13)	0.12
von Frey ongoing	2.5 ± 3.2	2.5 ± 3.3	-0.03 ± 1.9 (N=15)	0.95
von Frey sharpness	3.3 ± 2.5	3.9 ± 2.7	0.5 ± 4.1 (N=14)	0.64

The QST values are analysed as reversed Z-scores. No age and sex in the regression model.

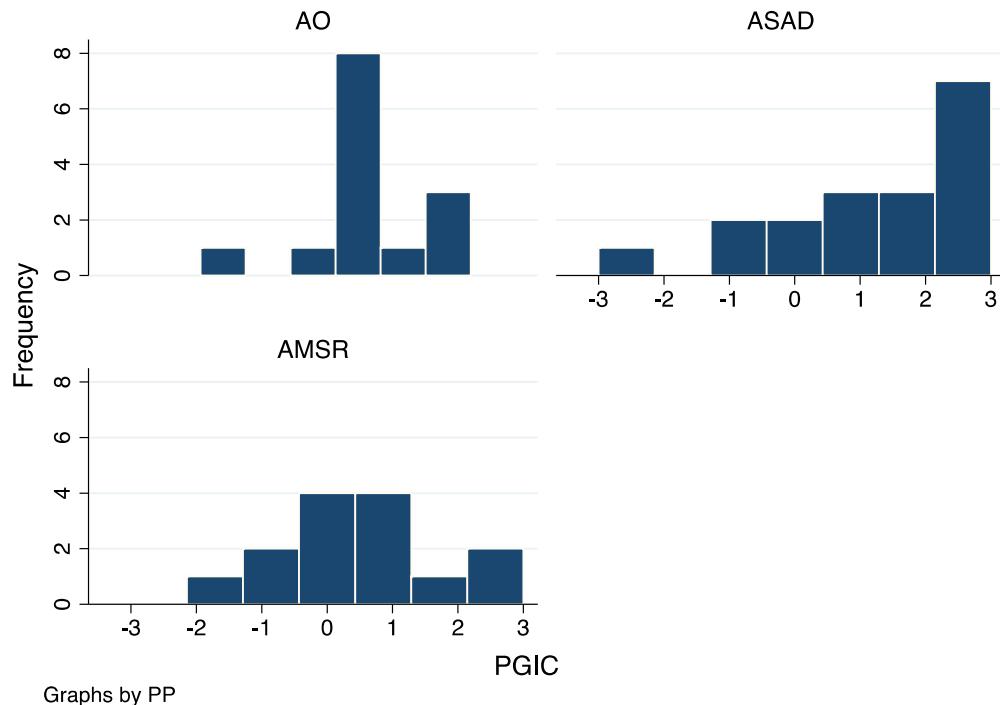
Supplementary Table 6 - Between-arm changes in clinical and psychophysical measures - per protocol analysis

PP	ASAD vs AO		ASAD vs AMSR	AO vs AMSR
	Outcomes	MD (95% CI) [p-value]	MD (95% CI) [p-value]	MD (95% CI) [p-value]
OSS	1.0 (-5.6, 7.6) [0.76]	4.86 (-1.23, 10.95)	3.86 (-3.07, 10.80)	
PPI	1.55 (-0.27, 3.38)	-1.90 (-3.48, -0.34)	-3.45 (-5.26, -1.64)	
PD-Q	0.22 (-3.26, 3.69)	-1.97 (-5.25, 1.31)	-2.19 (-5.81, 1.43)	
HADS	-0.17 (-4.52, 4.18)	-3.73 (-7.87, 0.40)	-3.56 (-8.08, 0.95)	
MDT affected	-0.079 (-0.36, 0.20)	-0.23 (-0.50, 0.044)	0.15 (-0.44, 0.14)	
MDT contralateral	-0.11 (-0.35, 0.13)	-0.18 (-0.41, 0.055)	-0.069 (-0.32, 0.18)	
MPT affected	-0.24 (-0.52, 0.05)	-0.09 (-0.37, 0.19)	0.15 (-0.16, 0.45)	
MPT contralateral	-0.22 (-0.46, 0.015)	0.016 (-0.21, 0.24)	0.24 (-0.0067, 0.48)	
PPT affected	-0.013 (-0.19, 0.16)	-0.014 (-0.15, 0.12)	-0.00082 (-0.17, 0.17)	
PPT contralateral	0.0090 (-0.12, 0.14)	0.02 (-0.093, 0.136)	0.012 (-0.12, 0.14)	
PPT sternum	0.074 (-0.05, 0.20)	-0.007 (-0.11, 0.09)	-0.08 (-0.20, 0.04)	
von Frey ongoing	-0.27 (-1.79, 1.26)	-0.95 (-2.41, 0.51)	-0.68 (-2.25, 0.89)	
von Frey sharpness	1.05 (-0.76, 2.85)	0.03 (-1.76, 1.82)	-1.02 (-2.90, 0.87)	

The QST values are analysed as log-transformed raw data. Age and sex were included in the regression model.

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Patient Global Impression of Change



Graphs by PP

Supplementary Figure 9 - Patient Global Impression of Change after treatment in each arm separately

Local maximum for activation in the patient and control group

Supplementary Table 7 - Patient group mean at baseline - local maxima of activation peaks

Cluster Index	Voxels	Z-MAX	Z-MAX X (mm)	Z-MAX Y (mm)	Z-MAX Z (mm)	MNI
5	42214	9.79	-61	-28	21	contralateral S2/parietal operculum, supramarginal gyrus
4	2531	7.06	-45	-49	-20	contralateral inferior temporal gyrus
3	1305	6.45	45	-40	-20	ipsilateral inf temporal gyrus
2	1061	6.75	-9	-78	39	contralateral precuneus

Supplementary Table 8 - Control group at baseline - local maxima of activation peaks

Cluster Index	Voxels	Z-MAX	Z-MAX X (mm)	Z-MAX Y (mm)	Z-MAX Z (mm)	MNI
5	45851	8.92	58	-24	20	ipsilateral S2/parietal operculum
4	770	5.57	-7	-76	45	precuneus
3	232	3.98	-9	-72	8	intracalcarine cortex
2	104	4.12	-23	41	-14	contralateral frontal pole
1	96	5.52	23	40	-12	ipsilateral frontal pole/frontoorbital cortex