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Central pain modulatory mechanisms of attentional analgesia are preserved in fibromyalgia

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ABSTRACT

Fibromyalgia is a prevalent pain condition that is associated with cognitive impairments including in attention, memory, and executive processing. It has been proposed that fibromyalgia may be caused by altered central pain processing characterised by a loss of endogenous pain modulation. We tested whether attentional analgesia, where cognitive engagement diminishes pain percept, was attenuated in fibromyalgia patients (n=20) compared to matched healthy controls (n=20). An individually calibrated, attentional analgesia paradigm with a 2x2 block design was used with brain and brainstem-focussed fMRI. Fibromyalgia patients had both lower heat pain thresholds and speeds in a visual attention task. When this was taken into account for both attentional task and thermal stimulation, then both groups exhibited an equivalent degree of attentional analgesia. fMRI analysis showed similar patterns of activation in the main effects of pain and attention in the brain and brainstem (with the sole exceptions of increased activation in the control group in frontopolar cortex and the ipsilateral locus coeruleus). The attentional analgesic effect correlated with activity in the periaqueductal grey and rostroventromedial medulla. These findings indicate that fibromyalgia patients can engage the descending pain modulatory system if the attentional task and noxious stimulus intensity is appropriately titrated.

Keywords: fibromyalgia; pain; fMRI; attention; brainstem; analgesia

INTRODUCTION

Fibromyalgia is a common, chronic condition characterised by widespread pain with hyperalgesia in muscles and joints without any identifiable alternative causative pathology [6,70,84]. In addition to widespread pain, fibromyalgia is syndromically-linked to fatigue, sleep deficits and difficulties in concentration, an array of symptoms which has been referred to as

"fibrofog" [43,81]. A single underlying pathophysiological cause for fibromyalgia is yet to be fully elucidated [69] and the current diagnostic criteria are based on self-reported measures [75,82,83].

There are a plethora of studies reporting alterations in nociception and pain processing in patients with fibromyalgia. One intriguing line of investigations has reported a small fibre deficit and altered function of nociceptive primary afferents [31,50,56,72,77] which may give rise to hyperalgesia. As a counterpoint theory, fibromyalgia has also been proposed to be a "centralised" pain condition [12] characterised by augmented brain responses to noxious stimuli that underlies hyperalgesia [15,30,66]. In support of a central aetiology of fibromyalgia, there have been reports of impairments in endogenous pain modulatory mechanisms, such as conditioned pain modulation [8,42,49] and exercise induced analgesia [80]. This has, in part, been the justification for the use of treatments to boost central pain modulatory circuits through the use of monoaminergic re-uptake inhibitors (increasing noradrenaline and serotonin) which are amongst the few medications with any evidence of efficacy in fibromyalgia [7,12].

Endogenous pain modulation [60] can also be engaged by cognitive manipulations, such as placebo analgesia [4,19] or a shift in attentional focus [3,78]. In healthy subjects, attentional analgesia has been shown to involve brainstem structures such as the rostral ventromedial medulla (RVM), locus coeruleus (LC) and periaqueductal grey (PAG) [9,59,76,78] that mediate a component of their pain modulatory effects via endogenous monoamines [53,60]. These brainstem regions are intrinsically challenging to image [11] and have been only sparsely investigated in fibromyalgia despite being implicated as part of the causative central pathology.

The known link between fibromyalgia and impaired cognitive performance in domains such as attention, memory and executive processing [16,26,29,68] provides a rationale to investigate a form of endogenous analgesia that is driven by cognitive focus i.e. attentional analgesia. We hypothesised that there would be a demonstrable deficiency in attentional analgesia in patients with

fibromyalgia, and further that whole-brain/brainstem optimised fMRI could determine where any deficit originated within the descending pain modulatory system or the attentional network.

METHODS

The study had ethical approval from the NHS South Central Oxford B Research Ethics Committee (reference 13/SC/0617). All subjects gave written informed consent for study participation. The study was undertaken in the Clinical Research and Imaging Centre at the University of Bristol (CRiCBristol).

Recruitment

Fibromyalgia patients were recruited from local pain management clinics by clinician referral and poster advertisements. Sex-matched, healthy control subjects were recruited using poster and email advertisements at the University of Bristol. All subjects were screened for participation by telephone prior to attending for their single session. To meet inclusion criteria, they required a confirmed clinical diagnosis of fibromyalgia for at least six months prior to entry into the study. Subjects were excluded if they had other chronic painful conditions, were pregnant, or had a history of neurological or major psychiatric illness. Additionally, for control subjects, the presence of significant medical disorder precluded participation. Standard safety inclusion/exclusion criteria for participation in MRI studies were also applied. All subjects completed the Widespread Pain and Symptom Severity index [82] to validate the fibromyalgia diagnosis for patients and to confirm the absence of fibromyalgia symptoms for control subjects.

A total of 54 subjects (32 patients, 22 controls) were screened for the study, of which 14 failed the screening (3 were left-handed, 9 were unable to attend, 1 was unable to lie flat in the scanner, 1 did not pass the MRI screening). Twenty right-handed fibromyalgia patients (mean age 43, range 25-60, 18 females) and twenty right-handed, healthy subjects (mean age, 35 years, range 20-59 years; 18 females) participated in the study. The healthy control subjects were 8 years younger on

average than the fibromyalgia patients (paired t-test, p=0.03). Patients were not required to alter their regular medications which included: non-opioid analgesics (n=13), opioids (9) tricyclic antidepressants/ Serotonin and Noradrenaline re-uptake inhibitors (n=11) and gabapentinoids (n=7).

Experiment

Written informed consent was taken and MRI safety questionnaires were completed on the day of study. The subjects were told that the experiment was to examine the interaction between pain and attention in the brain with no mention of the phenomenon of attentional analgesia to avoid generating an expectation with regard to the study purpose. The American College of Rheumatology (ACR) Widespread Pain and Symptom Severity index [82] was completed with the assistance of clinician experimenters. Assessments were also made using: Edinburgh Handedness Inventory [58]; PainDETECT [24]; the "Pain now" and "Pain on average" scales from the Brief Pain Inventory [13]; Hospital Anxiety and Depression scale (HADS, [87]) and Pain Anxiety Symptom Scales (PASS, [52]). Any medications taken in the 72 hours prior to the session were recorded for all participants.

Both groups had a thermal Quantitative Sensory Testing (QST) with a circular contact thermode (CHEPS Pathway, MEDOC, Israel) applied on the left volar forearm using a modified version of the standardised protocol and script [67] (that included warm detection threshold, heat pain threshold, cold detection threshold and cold pain threshold). Study participants also had pressure pain threshold assessment over the thenar eminence using an algometer (Somedic, Sweden). After a short comfort / snack break, participants moved on to the calibration for the fMRI experiment.

The experimental protocol was identical in structure to the one described in our previous studies [9,59]. Briefly, participants received thermal stimuli to their left forearm for 30s at either 36°C (**low** temperature) or 42-45°C (**high** temperature), and a pseudo-random series of 1 second long "spikes" of 2, 3 or 4°C above these temperatures were superimposed to minimise habituation to stimulation.

The **high** temperature stimulus was calibrated for each individual to identify the thermal stimulus that produced a 6 out of 10 pain score.

Participants were also calibrated for a rapid serial visual presentation (RSVP) attentional task [64], where they were presented with rapidly changing letters and numbers on a display screen and they were instructed to press a button when spotting the number 5. The task had two possible levels of difficulty (**easy** or **hard**). The task was individually titrated such that its speed of presentation (i.e. inter-stimulus interval, ISI) was performance matched to ability. Each participant's task performance was assayed over a range of ISIs (from 32 to 256 ms) by calculating d-prime (d'). The d' values were fitted with a sigmoidal function and used to estimate the presentation speed corresponding to a 70% task performance which was used for their **hard** task during the experiment.

The ISI for the **easy** task was set to:

- 192 ms if the subject's **hard** task ISI was < 96 ms
- 256 ms if the **hard** ISI was ≥ 96 & < 256 ms
- 384 ms if the **hard** ISI was = 256 ms

The fMRI experiment had a 2x2 factorial design with four combinations for task and temperature (**easy**|**high**, **hard**|**high**, **easy**|**low** and **hard**|**low**) and has been described in detail previously [9,59]. Each experimental block lasted 70 seconds (comprising a fixation period with only a cross on the screen (17s), brief instruction to spot the target amongst distractors (5s), RSVP task performance and concurrent thermal stimulus (30s), a further fixation period (10s) and finally a rating period to obtain pain score (8s)). The blocks were presented in pseudo-random sequence within sessions and across participants. Each combination was repeated 4 times giving a total of 16 blocks. Task performance (hits, misses and false alarms) was also recorded during the experiment.

MRI data acquisition

Brain images were acquired with a 3T Siemens Skyra whole-body MR system using the same acquisition sequences as our previous studies [9,59]. Briefly, subjects' heads were positioned within the 32-channel receive only head coil, and memory foam pads placed around the skull to help minimise movement. Following acquisition of localiser images, a sagittal T1-weighted MPRAGE volumetric scan was acquired with TE/TR = 2.28/2200ms, flip angle = 9° and resolution of 0.86 x 0.86 x 0.86mm, phase encoding direction = A-P, GRAPPA acceleration factor = 2. Functional imaging data were acquired with an echo planar imaging (EPI) sequence and GRAPPA acceleration factor = 2, TE/TR = 30/3000ms, flip angle = 90° and a resolution of 1.77 x 1.77 x 3.5mm. Finally, to correct image distortion in EPI data, a gradient echo field map was acquired with TE1/TE2/TR = 4.92 / 7.38 / 520 ms, flip angle 60°, resolution 3 x 3 x 3.5 mm. During the fMRI experiment, cardiac and respiratory waveforms were recorded using pulse oximeter and respiratory bellows for subsequent physiological noise modelling [11].

fMRI analysis

Functional images were pre-processed and analysed in FEAT (FSL version 6 [39]). The pre-processing pipeline was consistent with our previous papers [9,59] and included motion correction with MCFLIRT [38], fieldmap unwarping with FUGUE [37], registration to standard MNI template with FNIRT [1] and FLIRT [40], 4mm spatial smoothing and high-pass temporal filtering using a 90 s cut-off. The general linear model (GLM) in FEAT, part of FSL, was used to assess brain activation to the four experimental conditions (**easy|high**, **hard|high**, **easy|low** and **hard|low**) and nuisance regressors (task instruction, rating periods), which were convolved with a hemodynamic response function. The design also included temporal derivatives, local autocorrelation correction (FILM [85]) and a set of regressors modelling physiological noise [10,33].

Simple main effects were estimated by first creating difference contrasts between conditions at the first (i.e. subject) level e.g. (easy|high + hard|high) – (easy|low + hard|low) for the main effect of temperature, looking for regions more active during high temperature stimulation irrespective of

task difficulty. Note that the reverse contrast was also calculated. This process was repeated for the simple main effects of task, along with the interaction contrasts. Next, these difference contrast images were passed up to the second (i.e. group) level where one-sample t-tests were used for statistical inference (for pooled data) and two-sample t-tests (for estimation of group differences). For consistency, the same approach was used for both whole brain analysis with FEAT, and for masked analysis using RANDOMISE. The analysis approach taken is recommended by the developers of the FSL software package, as the GLM is not designed to model repeated measures in 2x2 factorial designs. Whole brain group differences were assessed with an one-sample t-test in FEAT using a mixed-effects model (FLAME) and cluster-based correction for multiple comparison (with cluster forming threshold $Z > 3.1$ and cluster corrected $p < 0.05$ to adjust for family-wise error, in accordance with the latest recommendations for spatial analysis of fMRI data [21]).

The brainstem focussed analysis was performed at the group level using a set of anatomical masks and statistical inference using permutation testing [55] in RANDOMISE (part of FSL). This analysis utilised pre-defined regions of interest based on previously defined probabilistic masks of the a priori specified brainstem nuclei (PAG, RVM, and left / right LC, defined previously [9]). A two-sample unpaired t-test design was built with GLM (in FSL) in accordance with FEAT guidance. The number of permutations were set to 10,000 in line with guidelines [21] and results reported using threshold free cluster enhancement (TFCE) corrected $p < 0.05$.

Where simple main effects or interactions were found in the imaging data, the nature of these differences was explored using FEATQUERY. Parameter estimates were extracted from each experimental condition (i.e. **easy**|**low** vs rest, **hard**|**low** vs rest, **easy**|**high** vs rest, **hard**|**high** vs rest) and their relationship to the individual behavioural responses examined.

The magnitude of attention-mediated analgesia was compared to BOLD signal change in the brainstem nuclei (PAG, RVM and LC) specified a priori (as per our earlier study [9]). Average pain ratings obtained during high temperature stimulation at the two different task difficulties were

subtracted (i.e. **easy|high – hard|high**) and demeaned to obtain a group-level covariate. The difference in the BOLD signal recorded for **hard|high** minus **easy|high** was correlated with the difference in pain ratings in an inter-subject parametric regression model. RANDOMISE was used to assess correlations in PAG, RVM, left and right LC masks. The latter analysis was done on the whole cohort (fibromyalgia patients and healthy controls).

All whole brain results (group means and group comparisons) are reported for $Z > 3.1$, cluster corrected $P < 0.05$. All brainstem results are reported for $P < 0.05$, TFCE corrected.

Questionnaire, QST and behavioural data analysis

All statistical analyses (questionnaires, QST, pain ratings, task performance) were carried out in SPSS (version 26). Unpaired t-tests were used on questionnaire results to detect differences between patient and control groups.

Hit rate (the proportion of correct responses to targets) and false alarm rate (the proportion of responses to non-targets) were calculated and z transformed. Subsequently, *d'* was calculated as the difference between z transformed hit rate and z transformed false alarm rate. The interstimulus intervals were compared with a Mann-Whitney U-test.

Pain ratings and task performance recorded during the fMRI experiment were analysed with a mixed ANOVA (with two within-subject factors: task and temperature, and one between-subjects factor: group). A pre-specified post hoc comparison of the difference in pain scores between the **easy|high** vs **hard|high** condition was undertaken to identify any attentional analgesic effect.

Prior to statistical analysis, data were examined for the presence of outliers, normality of distribution and equality of variance. Results are reported as mean ± standard deviation or median and [range] where appropriate. The indicative significance level was set to $P<0.05$ throughout.

RESULTS

Demographics

All patients met the ACR 2010 Diagnostic Criteria for fibromyalgia [82], scoring 13.5±2.6 on the Widespread Pain Index (WPI) and 10.0±1.5 [7-12] on the Symptom Severity (SS) scale score (WPI ≥7 and SS ≥5, Table 1). None of the healthy controls met the ACR 2010 Diagnostic Criteria, scoring 1.0±1.0 [0-3] on the WPI and 2.0±1.1 [1-4] on the SS (Table 1).

As expected, the fibromyalgia patients had higher ratings than the control group for the 'pain now' (5.3±1.6 vs 0.1±0.2 respectively, $P < 0.0001$) and 'pain average' (6.4±1.7 vs 0.7±1.0 respectively, $P < 0.0001$, Table 1) domains of the BPI. They also scored higher on the PainDETECT questionnaire compared to controls (15.7±8.2 vs 2.4±3.3 respectively, $P < 0.0001$, Table 1). Fibromyalgia patients had elevated anxiety and depression scores (12.2±3.6 and 10.5±4.7, with 17 and 15 patients scoring >8, respectively) in comparison to healthy controls (4.6±4.0 and 1.3±1.3, with 3 scoring >8 for anxiety) on the HADS ($P < 0.0001$ in both cases, Table 1). Fibromyalgia patients also had higher scores in the cognitive, avoidance, fear and anxiety sections of PASS (all $P < 0.0001$, Table 1).

Quantitative sensory testing

Patients with fibromyalgia exhibited hyperalgesia to thermal and deep pressure stimuli when compare to controls. The heat pain threshold was lower in fibromyalgia patients (41.6±4.6°C fibromyalgia vs 45.3±3.9°C controls, $P=0.01$, unpaired t-test, Figure 1A) and the cold pain threshold was at a higher temperature (fibromyalgia 25.7°C [1.7 – 32°C] vs healthy controls 4.5°C [0 – 30.6°C], $P = 0.001$, Mann-Whitney test, Figure 1B). Similarly, the pressure pain threshold was lower in the fibromyalgia patients (fibromyalgia 162±18 vs control 265±25 kPa, $P=0.0019$, unpaired t-test, Figure 1C). The warm detection threshold was higher in fibromyalgia patients (34.7°C [33.4 – 46.8°C] vs 33.9°C [33.3 – 36.2°C], $P = 0.016$, Mann-Whitney test Figure 1D).

There were two outliers in the fibromyalgia group and their exclusion reduced the difference in medians to 0.5˚C but the result remained significant (P=0.046). There was no difference in cold detection threshold (30.6°C [23.7 – 13.2°C] vs 30.6°C [26.8 – 31.4°C], P = 0.73, Mann-Whitney test).

Titration of thermal stimulation and task difficulty

The percept calibrated **high** (painful) thermal stimulus to be used during fMRI was set at a lower temperature for the fibromyalgia patients, which was in keeping with thermal hyperalgesia identified by baseline QST. The temperature eliciting a pain intensity rating of 6 out of 10 was 42±2°C for fibromyalgia patients and 43.1±1.7 °C for healthy controls (P=0.047, Figure 1E). The difficulty of the **Hard** RSVP task to be used during the experiment, was individually calibrated for each participant. Fibromyalgia patients required a longer interstimulus interval in the RSVP task to perform at 70% of optimal (fibromyalgia: 96ms [48 – 256ms] vs control: 64ms [32 – 96ms], P=0.008, Mann-Whitney test, Figure 1F).

Pain ratings during the fMRI experiment

The objective of the experiment was to examine whether the pain evoked by the thermal stimuli (**low** or **high** temperature) was affected by the concurrent performance of the RSVP attention task (**easy** or **hard** task). The behavioural data (pain scores) were initially pooled for both groups (Figure 2A). There was an expected main effect of temperature ($F(1,38) = 174.8$, $P < 0.001$, mixed ANOVA) and a temp*task interaction ($F(1,38) = 13.1$, $P = 0.001$, mixed ANOVA). There was no main effect of task ($F(1,38) = 2.6$, $P = 0.12$). A planned post-hoc analysis showed reduced pain in the **hard**|**high** (43.8±2.8) versus the **easy**|**high** (47.9±2.4) condition consistent with an attentional analgesic effect ($P = 0.001$, paired t-test).

In the pooled analysis there were no differences between the control and fibromyalgia groups (temp*group ($F(1,38) = 0.2$, $P = 0.65$); task*group ($F(1,38) = 4.7$, $P = 0.66$) or temp*task*group ($F(1,38) = 0.01$, $P=0.97$)). To illustrate the behavioural similarity between the control group and the fibromyalgia patients the results are plotted separately (Figure 2B-C). In healthy controls a main effect of temperature and a task*temp interaction was evident ($F(1,19) = 104.2$, $P < 0.0001$ and $F(1,19) = 11.9$, $P = 0.003$ respectively). Likewise, in fibromyalgia patients there was a main effect of temperature and a task*temp interaction ($F(1,19) = 73.9$, $P < 0.0001$, $F(1,19) = 4.6$, $P = 0.046$, respectively). For both groups, post-hoc paired t-tests revealed that the interaction was due to an attentional analgesic effect with a decrease in pain scores in the **hard**|**high** versus the **easy**|**high** condition.

Task performance in the fMRI experiment

To assess performance on the RSVP task during the fMRI experiment, the subject's button responses were recorded and used to calculate d'. We noted that controls performed the task better overall in the scanner as reflected in the between subject (i.e. group) effect ($F(1,38) = 10.2$, $P=0.003$) indicating that our initial calibration (outside the scanner) did not fully compensate for the differences in performance levels between the groups when they were challenged within the scanner (Figure 3). Importantly, and as intended, the hard task was more challenging than the easy task with both groups showing a main effect of task ($F(1,38) = 46.0$, $P < 0.0001$, mixed ANOVA, Figure 3). Fibromyalgia patients and controls showed a similar drop in performance when comparing the easy with hard tasks as there was no interaction between task performance and group, ($F(1,38) = 2.7$, $P = 0.11$). Further analysis indicated that stimulus temperature had no effect on task performance (main effect of temperature $F(1,38) = 0.2$, $P = 0.63$), and there was no interaction between task and temperature ($F(1,38) = 0.9$, $P = 0.34$), nor between temperature and group ($F(1,38) = 2.6$, $P = 0.12$).

Neuroimaging analysis

The behavioural results indicated that the fibromyalgia patients had thermal hyperalgesia and overall a lower level of performance on the RSVP task, but when these factors were mitigated by adjusting stimulus temperature to percept and task speed to performance (in the pre-scanner session), they could still produce attentional analgesia. However, it was not clear if they recruited the same brain networks as healthy controls to produce this analgesic effect. Therefore, the same analysis strategy used for the behavioural pain ratings was also applied to the fMRI data. To determine main effects in the patterns of activation in brain and the brainstem, data from both groups were pooled and subsequently differences between the subject groups was explored.

Whole brain analysis of the main effect of temperature in pooled group data revealed an expected pattern of activity in forebrain regions commonly seen in pain imaging studies including prominent clusters in the contralateral (i.e. right) dorsal posterior insula, primary somatosensory cortex and anterior cingulate cortices (Figure 4A, Table 2). Brainstem region-masked analyses showed a main effect of temperature in the RVM (Figure 4A). Analysis of group level differences in the whole brain response to temperature, showed no differences bar the singular exception of an enhanced response in healthy controls in the frontopolar cortex (Brodmann Area 10, Figure 4B, Table 2). Similar analyses in the brainstem showed a group level difference in the left LC, again with an enhanced response in healthy controls (Figure 4B). Imaging data available at: https://identifiers.org/neurovault.collection:9513.

To explore the possible origins of these differences we conducted an exploratory analysis based on the observed need to use a hotter **high** temperature stimulus for the healthy controls than for fibromyalgia patients (Figure 1E). Therefore, the correlation of BOLD signal change for each area (BA10 and LC) and difference between the **high** and **low** applied temperatures was calculated. The left LC BOLD signal showed a positive correlation with the difference between **high** and **low** temperatures (Pearson's R=0.48, P=0.02, Figure 4B), suggesting that the difference in applied

temperature might account for the group level difference. A similar analysis did not reveal any correlation between temperature delta and activity in BA10 (R=0.19, P=0.47).

Whole brain analysis of the main effect of task in the pooled data showed a familiar pattern of increased activity in the visual attention network including: lateral occipital cortex; superior parietal lobule, anterior insula and anterior cingulate cortex, and a decrease in activity in the precuneus and fronto-medial cortex (Figure 5A, Table 2). Brainstem region masked analyses showed a main effect of task in the PAG, RVM and left LC (Figure 5B). No difference between the fibromyalgia and control groups was detected in the main effect of task at whole brain or brainstem level. Imaging data available at: https://identifiers.org/neurovault.collection:9513.

No task*temperature or task*temperature*group interaction (that could be the neural substrate of the observed behavioural interaction between task and temperature i.e. attentional analgesia) was seen at the whole brain or brainstem level.

A planned analysis sought correlations between the fMRI data (individual BOLD differences between **hard**|**high** and **easy**|**high** conditions) and the change in pain scores (i.e. analgesic effect, **easy**|**high** minus **hard**|**high**) to improve the power to identify possible neurobiological substrates of the analgesic effect [9,59]. The whole brain regression analysis (i.e. inter-subject) did not identify any significant regions showing correlation. However, masked brainstem analyses with the same model showed a positive correlation between analgesic effect and the change in activity in both the PAG and the RVM (Figure 6).

DISCUSSION

In this study we demonstrate that, contrary to our expectation at the outset, fibromyalgia patients can produce attentional analgesia with similar efficacy to healthy volunteers. Analysis of the pain ratings during the fMRI experiment revealed that diversion of attentional focus attenuated the pain reported in response to a hot thermal stimulus. This result is in contrast to previous evidence of malfunctioning endogenous pain modulation in fibromyalgia [42,44,48,74,80]. The specific exemplar of conditioned pain modulation has consistently been found to be impaired in fibromyalgia patients [8,32,62,65,71], up to the point of becoming a test used for the evaluation of novel pharmaceutical therapies [86]. It should be noted however that two previous reports have provided some evidence that attentional analgesia may be preserved in fibromyalgia patients. Evoked pain was decreased while performing a Stroop task [22,51]. Although neither study was able to show significant difference in pain scores (i.e. analgesia) between the easy (congruent) and hard (incongruent) version of the Stroop task. By controlling for task performance, we can identify that it is the cognitive task difficulty that is modulating pain percept and so demonstrate that this form of attentional pain modulation is intact in fibromyalgia patients.

Other types of endogenous pain modulation such as placebo and music also produce some pain relief in fibromyalgia patients [23,27,34,61], although with lower efficacy in patients with a longer disease duration [45]. It therefore seems that cognitive modulation of pain more generically is functional in fibromyalgia and this may be a point of difference with conditioned pain modulation which is mediated by more of a hindbrain mechanism without a need for cortical drive. It has been proposed that the lack of analgesia induced by exercise or by a conditioned stimulus in fibromyalgia is caused by the engagement of pain facilitatory networks [32,41,48]. Another possibility is that the cortex-brainstem-spinal cord modulatory system is disrupted in fibromyalgia patients and that they are only able to achieve analgesia by forebrain processes. The latter hypothesis was motivated by

the finding of unchanged spinal withdrawal reflex during placebo analgesia, despite the reduction in pain scores, suggesting that the spinal cord activity was not modulated [27] however this is at odds with other studies of placebo analgesia in healthy volunteers that have demonstrated a clear spinal modulation using fMRI [18,19]. These contrasting findings with placebo analgesia raise the question of whether attentional analgesia in fibromyalgia patients is mediated by engagement of descending control mechanisms as has been reported in healthy subjects [9,59].

To resolve the brain regions involved in attentional analgesia, we used the same brainstem optimised imaging strategy as in our previous studies [9,59]: the analgesic effect in both groups correlated with the BOLD change PAG and RVM. This showed a positive linear relationship with the analgesic effect and suggests that these regions are mediating attentional analgesia. This is consistent with the proposition that fibromyalgia patients can indeed recruit the descending pain modulatory system to generate attentional analgesia. Conclusive, direct evidence that PAG and RVM modulate the spinal cord during attentional analgesia is not yet present, but it has been repeatedly suggested [9,59,73,76]. Functional imaging of brainstem and spinal cord during an endogenous analgesia paradigm would help clarifying this issue by determining whether attentional analgesia is mediated by descending control from brainstem to spinal cord to regulate nociception.

Quantitative sensory testing revealed thermal hyperalgesia in fibromyalgia patients in response to both hot and cold stimuli, which is similar to that previously reported by other research groups [5,8,36,65]. We also saw an apparently conflicting small increase in warm detection threshold without a change in cold detection threshold in fibromyalgia patients. These slightly contradictory findings could fit with the proposition that this is due to altered functioning in primary afferents due to a latent small fibre neuropathy [17,77] and hyperexcitable C-nociceptors [72]. On the other hand, recent evidence from a laser evoked potential study, failed to reveal the expected abnormal responses in fibromyalgia patients [2]. In our study, by carefully percept-locking our thermal

stimuli we took account of the altered sensitivity between the groups and the data from our imaging protocol does not shed any further light on this ongoing debate.

An alternative hypothesis regarding the aetiology of fibromyalgia is that the hyperalgesia is be due to altered central processing [12,15,30,66]. In support of this idea, it is worth noting that aberrant sensitivity is found in fibromyalgia patients in many body locations and across sensory modalities (e.g., thermal and mechanical pain [5]). Our results indicate that the fibromyalgia patients show a similar pattern of brain activation to the healthy controls in response to the percept-matched thermal stimulus (like Gracely *et al.* [30]) and there was no group difference in BOLD in response to task difficulty. However, we did find a difference between fibromyalgia patients and controls in the anterior prefrontal cortex (BA10) and in the left locus coeruleus in the main effect of temperature. Interestingly, the BOLD change in the LC correlated with the temperature used for the attentional analgesia experiment. Animal and human studies have shown that the LC is activated by noxious thermal stimuli [35,59]. A similar relationship between human LC activity and thermal stimulus intensity has been made using pupillometry in healthy subjects [20]. Therefore, it is possible that the difference in LC activity in this contrast is due to the patients receiving a significantly lower temperature compared to controls (to achieve the same pain score). On the other hand, the BOLD signal difference between the groups in BA10 does not correlate with applied temperature but is possibly related to cognitive aspects of pain perception [63]. This region has been found to consistently respond to painful stimulus in healthy volunteers using a variety of imaging modalities (e.g. fMRI, NIRS and PET [63]) and it was reported that patients with fibromyalgia show reduced grey matter density in this and in adjacent cortical regions [47]. We also note a previous study comparing the response to pressure stimulation showed an area that was more active in control subjects than fibromyalgia patients that includes BA10 [30]. In addition, grey matter density in this area was reported to correlate negatively with the intensity of chronic pain [25,46,54,57]. Thus, this region is hypothesized to be important in the chronification of pain, although its role in this context

is yet to be fully elucidated [63]. Therefore, the difference between the groups in BA10 activity in our study may well relate to the impact of an ongoing level of spontaneous pain (chronically present) seen in the fibromyalgia patients that is not seen in the healthy controls. Our experimental design cannot demonstrate whether this is causally related. Overall, our findings do not provide evidence of substantial abnormalities in central pain processing in the fibromyalgia group and indeed show that the nociceptive processing as well as the engagement of descending control centres have many similarities.

We calibrated the hard version of the attentional task for each participant with the objective of achieving comparable cognitive load within and between groups (as per our previous studies [9,59]). We found that the inter-character presentation interval was significantly longer in the fibromyalgia group compared to healthy controls. This is in line with previous findings reporting prolonged reaction times in the fibromyalgia group in, for example, a Stroop task [51,79] and supports the evidence of impaired attentional/cognitive processes in fibromyalgia patients. It has been proposed that such behavioural impairments are reflected by abnormal functioning of the caudate nucleus and hippocampus [51], a finding that is not reproduced in the present study, which is to be expected because we adjusted task difficulty between the groups to produce equivalent performance which would mask any differences. Interestingly however, during the experimental phase the fibromyalgia patients performed worse than controls. This result may be consistent with the observation that painful stimulation has a disruptive impact on the cognitive ability of patients, possibly because of hypervigilance and catastrophizing [2,14,22,28]. Nevertheless, it is important to note that even during the experiment, a contrast in performance between easy and hard task was present in fibromyalgia patients. Indeed, the perceived difference in difficulty between the hard and easy task was homogeneous between groups, as evidenced by the absence of group difference in the main effect of task and both cohorts engaged the attentional network to a comparable degree.

A limitation of this study is that we were not able to precisely age match the control subjects with the fibromyalgia patients and by chance ended up with a significantly younger control group (by 8 years on average). Exploration of the influence of age, by inclusion as a covariate, in the analysis of the main effects of task and temperature and their interaction on pain scores, the heat and cold pain thresholds, and upon task performance in experiment did not substantially change the significance of any of our findings and so we do not believe that the difference in ages between the groups accounted for our findings.

In conclusion, the present study demonstrate that fibromyalgia patients are able to produce analgesia when engaged in a task that diverts their cognitive focus from a noxious stimulus. To this end, they engage brainstem nuclei in the same manner as healthy controls. This new evidence suggests that, contrary to what was believed, at least some of the elements of the pain descending modulatory system are functional in fibromyalgia patients and are available to be recruited. This also lends weight to the idea that therapeutically encouraging fibromyalgia patients to participate in cognitively engaging activities (as part of a multimodal rehabilitation package) may represent a useful therapeutic strategy as it may both aid their cognitive function and engage their descending pain control circuits to prioritise task performance.

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Supplemental video content

A video abstract associated with this article can be found at http://links.lww.com/PAIN/B376.

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FIGURES

Figure 1. Quantitative Sensory Testing and calibration. Quantitative Sensory Testing showed patients with fibromyalgia had smaller A) heat pain thresholds B) cold pain threshold and C) pressure pain threshold. D) The fibromyalgia patients also have an elevated warm detection threshold. E) The thermode temperature used for the **High** thermal stimulus was lower in the fibromyalgia patients. F) The inter-character interval for the RSVP task was longer in the fibromyalgia patients. Data presented as mean±SEM and comparison between groups with unpaired t-test except for C,D&E which are Median [IQR] and analysed with Mann-Whitney test (* - P<0.05, ** - P<0.01).

Figure 2. Pain ratings during the attentional analgesia experiment. A) Pain ratings for each subject across experimental conditions (easy and hard task and low and high temperatures) pooled across groups (n=40) and the same data is shown B) split into fibromyalgia patients (n=20) and C) healthy controls only (n=20). Mixed ANOVA showed a main effect of temperature and a task*temperature interaction mediated by a reduction in the pain scores in the Hard| High condition (planned post hoc paired t-test). Mean±SEM. (*** - P<0.001)

Figure 3. Task performance during the attentional analgesia experiment. Task performance (d') in the scanner showing that the hard task was more challenging than the easy task for both (A) fibromyalgia patients and (B) healthy controls. Mean±SEM. (Mixed ANOVA, Main effect of task - *** - P<0.001).

Figure 4. Main effect of temperature. Main effect of temperature in fibromyalgia patients and healthy controls in the whole brain, showing activity in dorsal posterior insula (dpIns), anterior cingulate cortex (ACC) and primary somatosensory cortex (S1) among others (Z>3.1 cluster

corrected P < 0.05), and in the Rostroventromedial medulla (RVM, TFCE corrected P < 0.05). B) Group difference in the main effect of temperature in the whole brain, showing a stronger response in healthy controls in both Brodmann area 10 (BA10, Z>3.1 cluster corrected P < 0.05) and in the left Locus Coeruleus (LC, TFCE corrected P < 0.05). The correlation between main effect of temperature in LC and difference in temperatures between low and high (Pearson's R = 0.49, P = 0.002, dotted 95% confidence interval). Abbreviations: OPC – Operculum, Pcu – Precuneus.

Figure 5. Main effect of task. Main effect of task in the pooled data from fibromyalgia patients and healthy controls (A) in the whole brain, showing increased activity in lateral occipital cortex (LOC), anterior insula (aIns) and anterior cingulate cortex (ACC) (red-yellow), and a decrease in activity in precuneus (Pcu), lateral occipital cortex and the frontomedial cortex (FMC, Z>3.1 cluster corrected P < 0.05). (B) Main effect of task in the brainstem: in the Periaqueductal gray (PAG), RVM and left LC (TFCE corrected P < 0.05). Abbreviations: SPL – superior parietal lobule.

Figure 6. Direct relationship between BOLD and analgesia. Activity in the PAG and the RVM correlates with the attentional analgesic effect. Inter-subject parametric regression between BOLD in PAG and RVM with the analgesic effect (i.e. delta pain ratings of **easy|high** – **hard|high)**, (p < 0.05, TFCE corrected).

Questionnaire	Fibromyalgia patients	Healthy controls	Significance
Widespread Pain Index (ACR)	13.5±2.6	1.0±1.0	N/A
Symptom Severity (ACR)	10±1.5	2±1.1	N/A
Pain now (BPI)	5.3±1.6	0.1±0.2	P < 0.0001
Pain on average (BPI)	6.4±1.7	0.7±1.0	P < 0.0001
PainDETECT	15.7± 8.2	2.4±3.3	P < 0.0001
Hospital Anxiety (HADS)	12.2±3.6	4.6±4.0	P < 0.0001
Hospital Depression (HADS)	10.5±4.7	1.3±1.3	P < 0.0001
Pain anxiety symptom (cognitive)	18.4±4.3	5.3±6.6	P < 0.0001
Pain anxiety symptom (avoidance)	14.6±5.6	5.8±5	P < 0.0001
Pain anxiety symptom (fear)	11.2±6.8	1.6±1.9	P < 0.0001
Pain anxiety symptom (anxiety)	11.6±5.5	1.5±2.4	P < 0.0001

Table 1. Results of questionnaires in fibromyalgia patients and healthy controls. All comparisons with unpaired t-test with the exception of PAS which is a one way ANOVA with Sidak's post hoc tests.

Voxels	Z Max	X (mm)	Y (mm)	Z (mm)	Atlas labels
Main effect of temperature pooled groups					
2676	7	42	-12	8	83% Central Opercular Cortex
1605	4.86	0	-74	-14	100% Vermis VI
1292	6.09	-36	4	8	66% Central Opercular Cortex
238	4.58	2	-62	54	69% Precuneous Cortex
166	4.87	24	-40	70	39% Superior Parietal Lobule, 33% Postcentral Gyrus
156	4.19	-20	-84	-38	100% Left Crus II
121	4.48	0	30	28	70% Cingulate Gyrus, anterior division, 13% Paracingulate Gyrus
90	4.23	-54	-30	18	70% Parietal Operculum Cortex, 6% Central Opercular Cortex, 6% Supramarginal Gyrus, anterior division, 5% Planum Temporale
85	4.81	-48	-66	-30	81% Left Crus I
84	4.53	-4	22	44	78% Paracingulate Gyrus, 7% Superior Frontal Gyrus
79	4.73	2	-10	44	73% Cingulate Gyrus, anterior division, 17% Cingulate Gyrus, posterior division
77	4.16	-50	44	-10	83% Frontal Pole
73	3.85	-20	-88	-24	13% Occipital Fusiform Gyrus, 66% Left Crus I
72	4.11	16	-14	6	97% Right Thalamus
65	4.34	30	-26	62	39% Postcentral Gyrus, 27% Precentral Gyrus
62	3.93	4	-6	12	34% Left Thalamus
62	4.71	-28	-50	-48	70% Left VIIIa, 14% Left VIIb
58	3.98	-38	62	8	54% Frontal Pole
56	3.77	-54	-52	48	46% Angular Gyrus, 33% Supramarginal Gyrus, posterior division, 5% Lateral Occipital Cortex

Group differences in main effect of temperature (Controls > Patients)					
124	3.98	-22	60	18	71% Frontal Pole
58	3.87	20	54	16	45% Frontal Pole
Main effect of task – pooled groups					
4234	6.22	-30	-94	8	5% Lateral Occipital Cortex
3671	6.68	34	-86	4	21% Lateral Occipital Cortex, inferior division
1147	6.27	8	28	30	48% Paracingulate Gyrus, 22% Cingulate Gyrus, anterior division
887	5.47	32	24	2	54% Frontal Operculum Cortex, 11% Inferior Frontal Gyrus, pars opercularis, 5% Inferior Frontal Gyrus, pars triangularis
382	5.53	-30	28	-2	54% Insular Cortex
273	5	-48	0	32	43% Precentral Gyrus, 12% Middle Frontal Gyrus, 11% Inferior Frontal Gyrus, pars opercularis
182	4.03	-4	-42	-20	43% Left I-IV
156	4.26	28	-52	54	43% Superior Parietal Lobule, 12% Angular Gyrus
155	4.96	-8	-70	-16	98% Left VI
140	5.27	4	-30	-4	70.9% Brain-Stem
130	4.59	-54	-20	2	51% Planum Temporale, 10% Heschl's Gyrus (includes H1 and H2)
104	4.25	-8	-74	-38	64% Left Crus II, 31% Left VIIb
54	3.75	-24	-68	-54	92% Left VIIb
Negative main effect of task – pooled groups					
691	4.59	-6	-60	30	62% Precuneous Cortex
360	4.7	-38	-72	46	71% Lateral Occipital Cortex, superior division
248	4.95	52	-62	42	66% Lateral Occipital Cortex, superior division, 15% Angular Gyrus

Table 2. Results from main effect analyses in the whole brain obtained with cluster-forming threshold Z>3.09 and cluster-corrected p<0.05. The tables were created with Autoaq (part of FSL), with atlas labels based on the degree of overlap with probabilistic atlases (Harvard Oxford Cortical Structural Atlas, Harvard Oxford Subcortical Structural Atlas, Cerebellar Atlas in MNI152 space after normalization with FNIRT). Only those structures to which the cluster had a >5% chance of belonging to are presented.

Figure 1

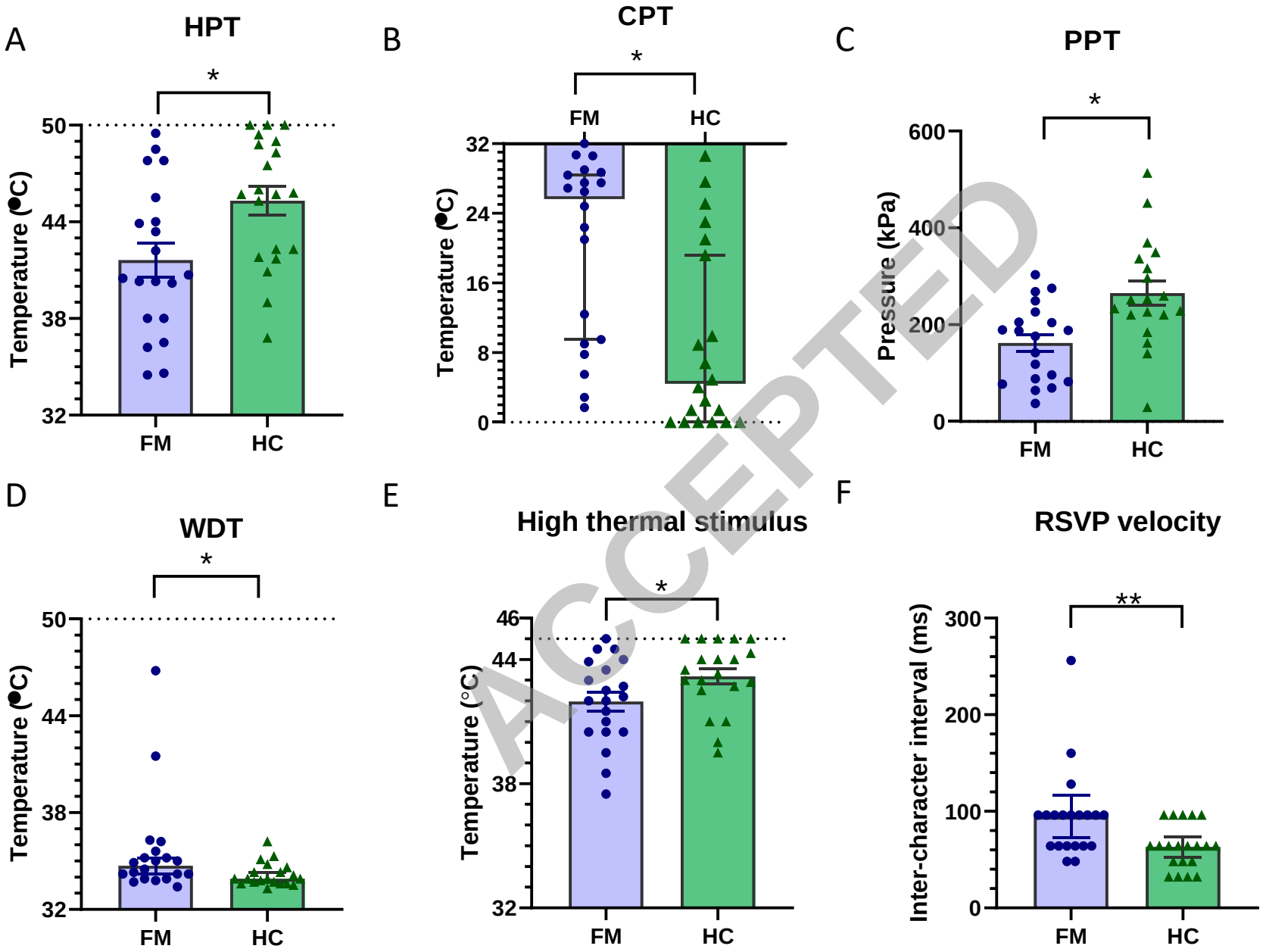


Figure 2

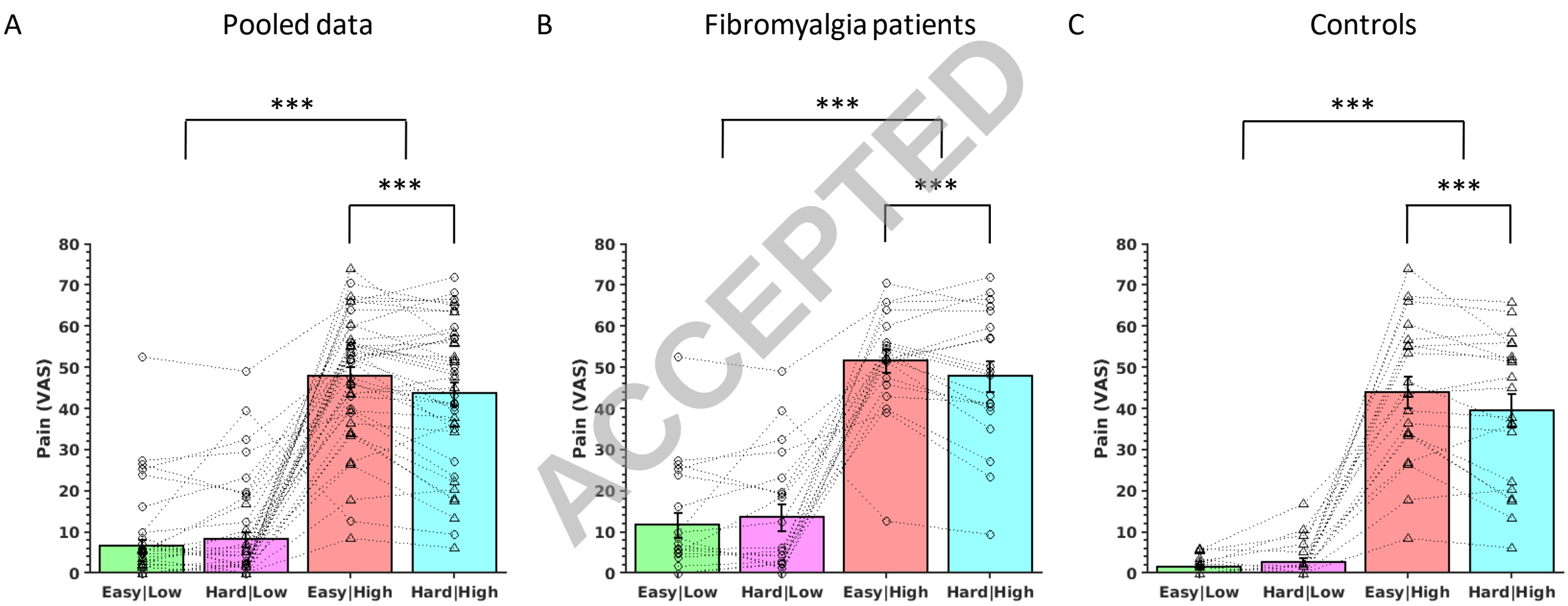
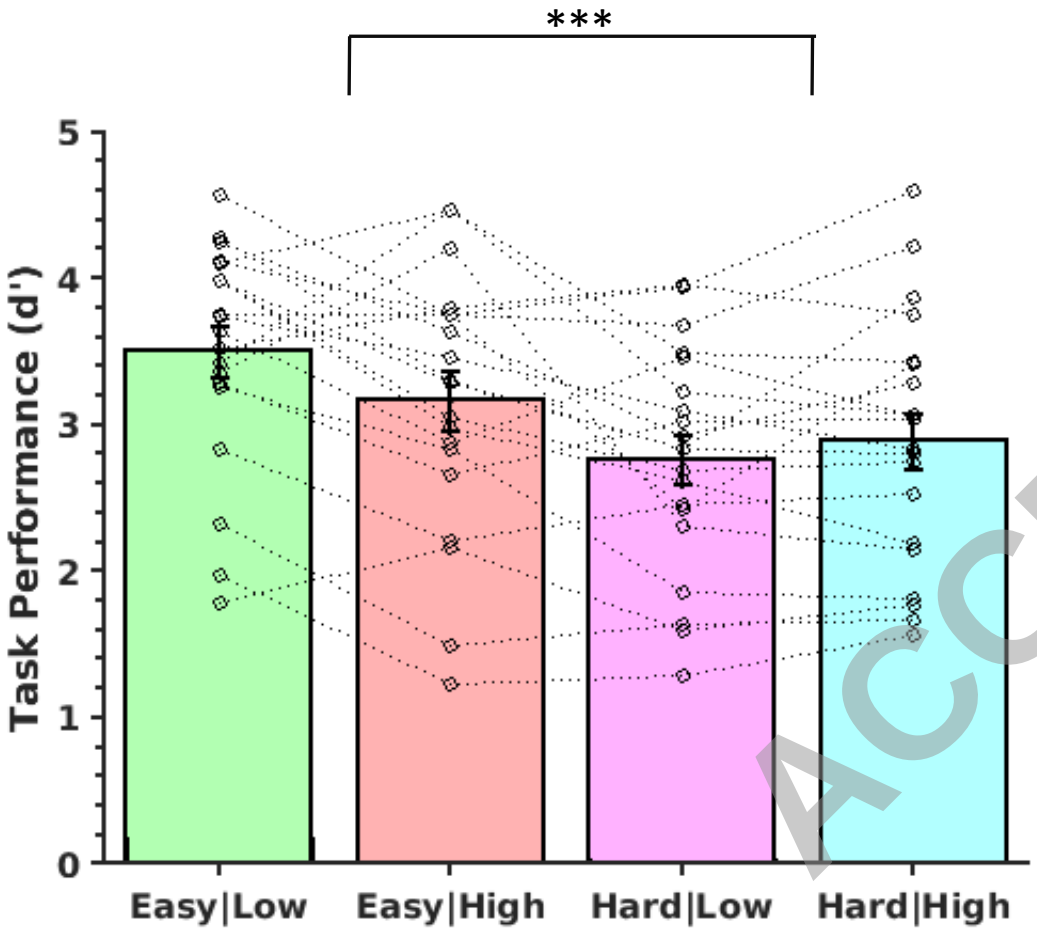


Figure 3

A Fibromyalgia patients



B Controls

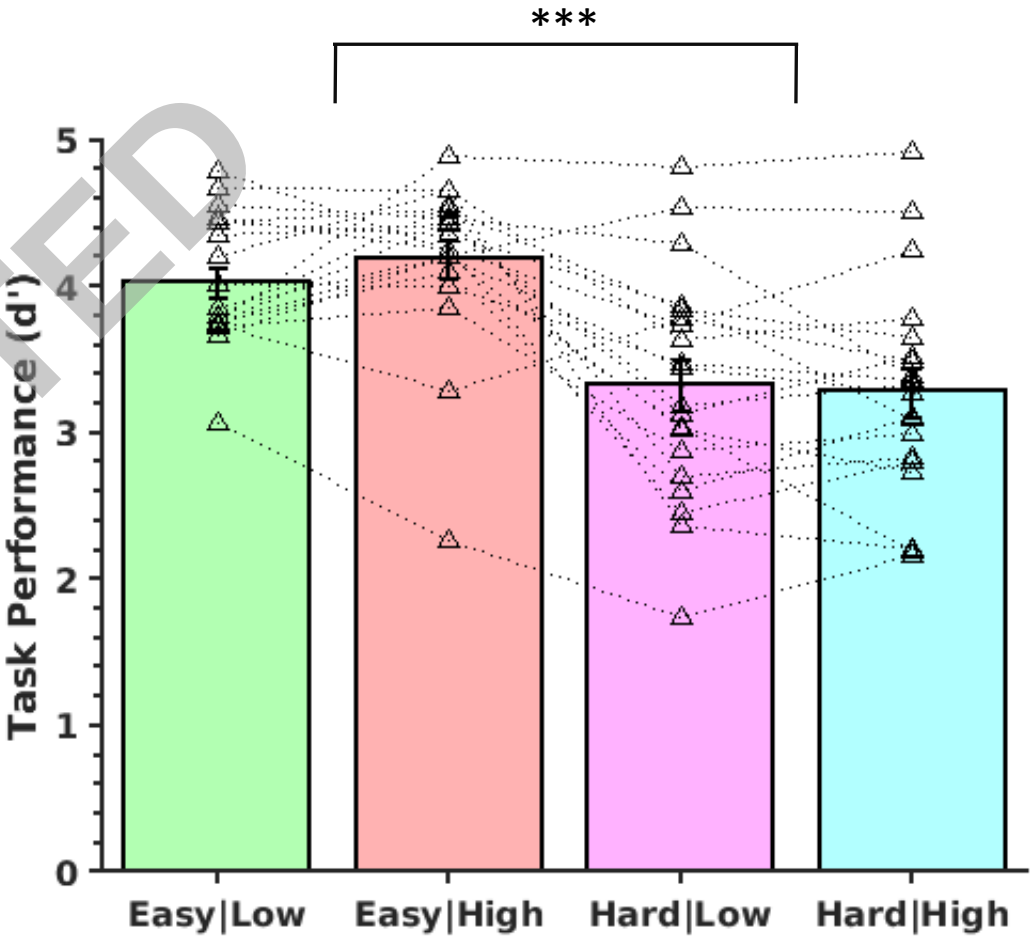
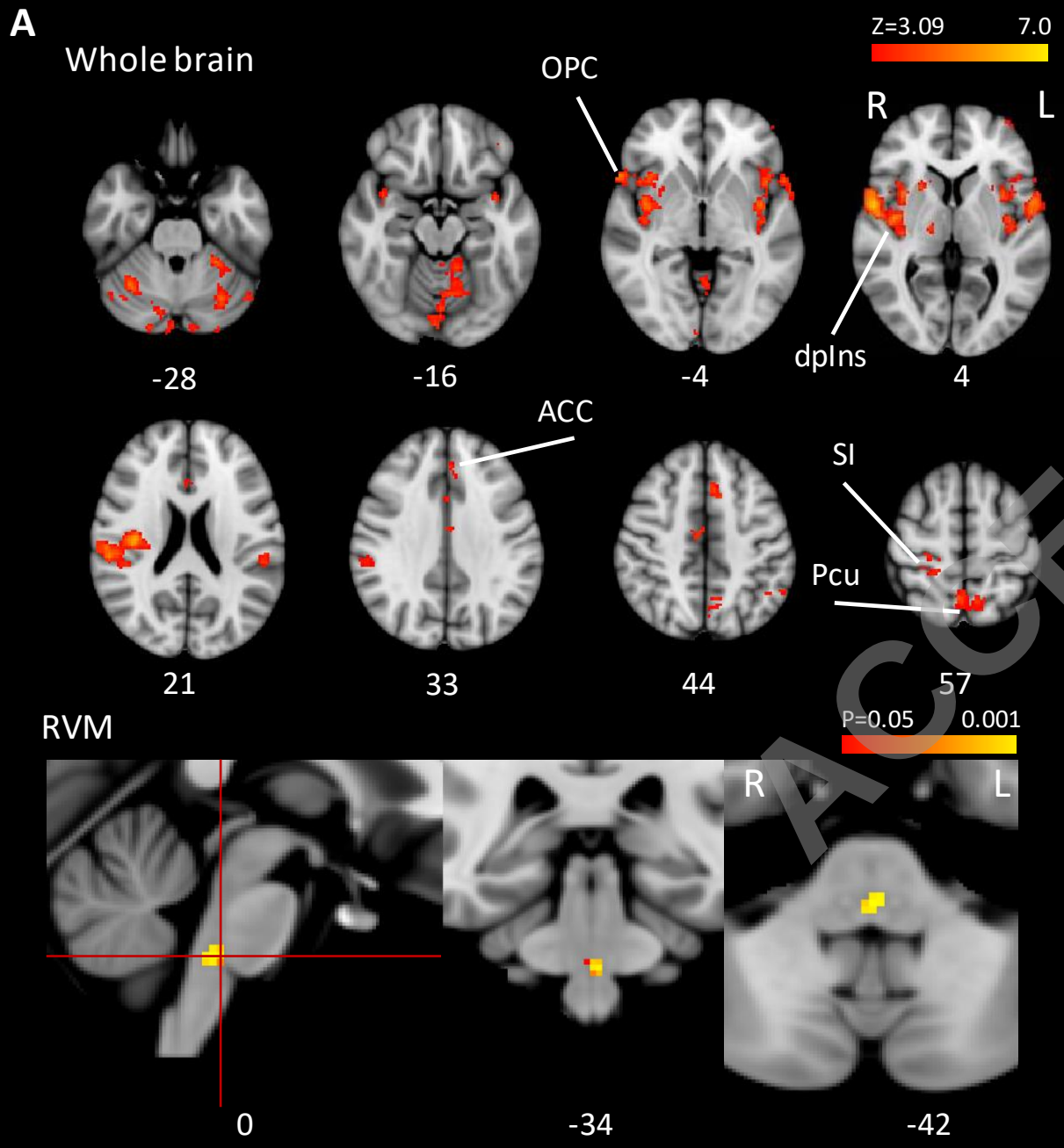


Figure 4

Main effect of temperature – FM and HC pooled



Main effect of temperature – Group differences

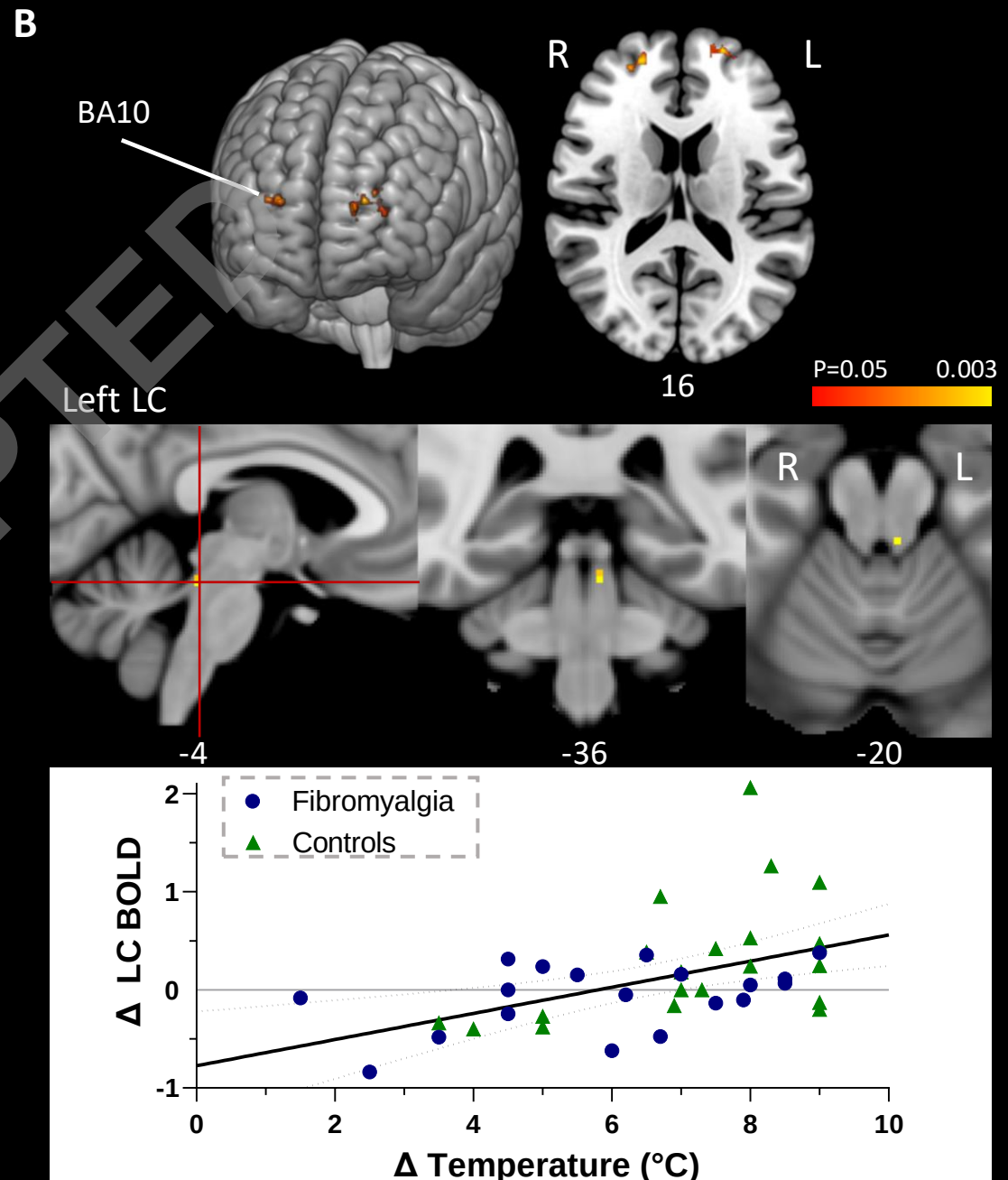


Figure 5

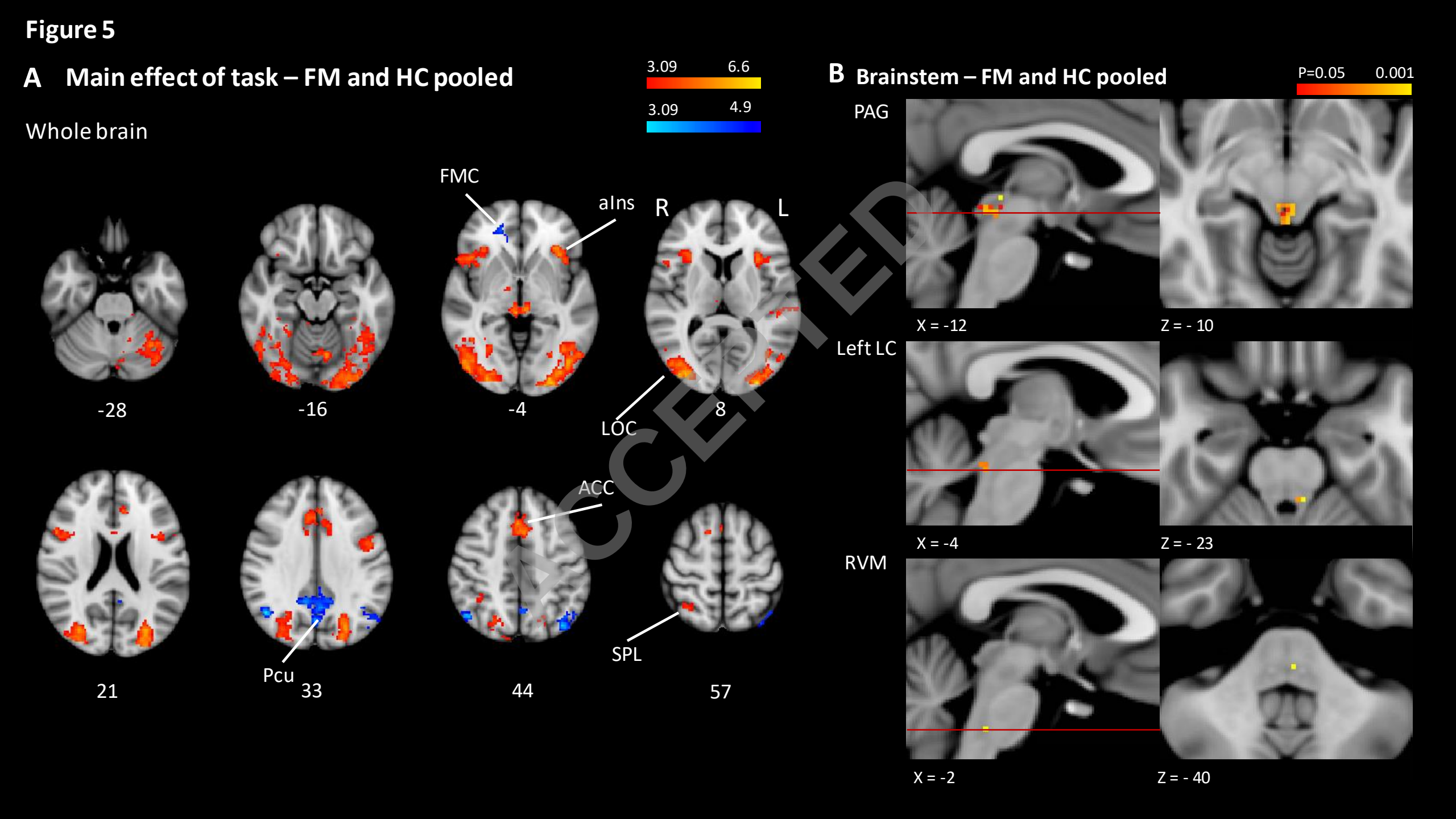


Figure 6

Correlation with analgesic effect

PAG

RVM