Individuals with chronic pain have the same response to placebo analgesia as healthy controls in terms of magnitude and reproducibility

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Abstract

It is unclear whether a diagnosis of chronic pain is associated with an increase or decrease in the placebo response. The aim of this study was to use an experimental placebo conditioning paradigm to test if expectancy for pain relief impacts on acute pain perception in individuals with a chronic pain diagnosis of osteoarthritis (OA) or fibromyalgia (FM), compared to healthy individuals (HI). An inert cream was applied to the dominant forearm of participants (60 OA, 79 FM and 98 HI), randomly assigned to either a placebo or control group. In both groups an inactive cream was applied to the dominant forearm. The placebo group was told this may or may not be a local anaesthetic cream, while the control group was told the cream was inactive. Laser pain was delivered, and numerical pain intensity ratings collected before, during and after cream application, along with expectation of pain relief and anxiety. The procedure was repeated two weeks later to assess reproducibility. There was a significant reduction in pain in the placebo group, independent of clinical diagnosis. Diagnostic groups (OA,FM,HI) did not differ in their magnitude of placebo analgesia or expectancy of pain relief. The results were similar in the repeat session. The results demonstrate that individuals with chronic pain respond to experimental placebo analgesia in a similar and reproducible manner as healthy individuals, despite higher levels of psychological co-morbidity. This has implications for utilising placebo analgesia in the treatment of chronic pain.

Introduction

Chronic pain carries a huge socioeconomic burden and substantially impacts the quality of life of affected individuals [13]. The lack of effective treatments for chronic pain, combined with our clearer understanding of underlying neurophysiological processes, has led to current research switching its attention from peripheral to central pain processing [41]. There is evidence of dysfunction within the endogenous pain inhibition system in most chronic pain syndromes [22,43]. This has resulted in the investigation of alternative techniques to utilise endogenous pain control mechanisms, for example placebo analgesia, which has been shown to have a significant impact on the subjective perception of pain [30].

The placebo effect, previously considered to be a nuisance variable, has since been shown to have substantial potential to improve patient outcomes [10]. Several commonly investigated techniques are used to induce placebo analgesia, with classical conditioning and manipulation of expectation being the most prominent [29].

In healthy individuals, placebo analgesia can be induced using a conditioning technique whereby the application of a sham anaesthetic cream is paired with the surreptitious lowering of an experimental pain stimulus. We and others have shown measurable and stable physiological and behavioural changes following such placebo (sham) treatments [14,31,46,47,53,54]. Placebo analgesia is reproducible in healthy individuals, and placebo responders tend to display particular cognitive traits, such as higher levels of dispositional optimism and reduced levels of state anxiety [33].

It has been suggested that placebo analgesia may be mediated by reduced negative emotional processing [3,4,35]. Pain normally increases negative emotions, which in turn increases the subjective experience of pain [37]. Conversely, analgesic administration induces the expectation of reduced unpleasant symptoms, which reduces anxiety and, consequently, actual symptoms of unpleasantness [3,4,15,38]. Chronic pain patients have psychological co-morbidities such as anxiety, depression, pain catastrophizing [32,48] and cognitive impairments [8]. For this reason, several models examining the role of expectancy and anxiety in modulation of pain by placebo have predicted reduced placebo analgesia in patients with chronic pain when compared to healthy individuals [33,35,32,48].

Existing data, however, shows that high levels of psychological co-morbidity do not affect the response to placebo in patients with chronic low back pain [5], and one study showed enhancing expectation improved the analgesic effects of acupuncture treatment in individuals with osteoarthritis [24]. In fact, a recent meta-analysis suggests individuals with chronic pain respond better to placebo analgesia than healthy individuals [16]. However, it should be noted that this conclusion was based on comparing average effect sizes from studies containing either pain patients or heathy individuals, but not having both groups within the same study.

In this study we aimed to examine the behavioural response to placebo analgesia in individuals with Osteoarthritis and Fibromyalgia when compared to pain-free healthy individuals, using a standardised, 2-stage conditioning technique (verbal suggestion and the adjunctive procedure of sham analgesic cream application), to optimise the analgesic effect. Furthermore, we explored

the reproducibly of a placebo effect in individuals with chronic pain over two sessions and explored the dependency of the placebo effect on the conditioning procedure.

Methods

Participants

The study was approved by the Greater Manchester West NRES Committee and the University of Manchester Ethics Committee. 60 patients with osteoarthritis (OA) and 79 patients with fibromyalgia (FM) were recruited from the Musculoskeletal Pain Clinics throughout the North West of England and from primary care practices that are part of the North West Primary Health Care Research Network. 98 pain-free healthy individuals (HI) with no history of ongoing pain symptoms were also recruited. Fibromyalgia patients fulfilled the 2010 American College of Rheumatology (ACR) criteria for the diagnosis of FM [53]. OA patients were diagnosed according to the standard ACR criteria [1]. All participants were over the age of 18, with no diagnosed neurological or morbid psychiatric illness, no peripheral vascular disease and no allergies to local anaesthetic creams (such as EMLA). Written informed consent was obtained prior to participation in the study. Handedness was not part of the inclusion criteria as we expected a typical distribution of left verses right handers.

Design

The experimental design included both between-subject factors and within-subject factors. Between-subject factors were the diagnostic categories (OA, FM, and HI) and whether the participant underwent the placebo (sham) treatment or a control experiment with no treatment. Regarding the treatment factor, participants within each of the three diagnostic categories (OA, FM, and HI) were randomized into one of two experimental groups: a Placebo (P) group or a control (C) group, undergoing either an experimental placebo procedure or a control procedure respectively on the right arm (see Figure 1 for details). Within-subject factors included the treatment session (1 and 2, on separate days) and the phase of the experiment (pre-conditioning, conditioning and post-conditioning).

Randomisation: Participants were randomised into treatment and control groups with a 2:1 ratio respectively. This imbalanced design sought to ensure that there were a sufficient number of participants in each of the sham-treated diagnostic sub-groups (minimum 35 per sub-group based on a power calculation) to obtain robust estimates of the intra-cluster correlation coefficient for each, while also allowing for attrition or other causes of data loss.

Laser stimuli

Laser heat stimuli (with a duration of 150 ms and a beam diameter of 15 mm) were applied to the dorsal surface of the both right and left forearms using a CO_2 laser stimulator. Between each pulse there was an inter-stimulus-interval of 10s. After each stimulus the laser was randomly moved over an area of 3 × 5 cm to avoid skin damage, habituation or sensitisation. The participants were asked to rate the stimuli verbally using a 0–10 Numeric Pain Rating Scale

(NRS) with 0 corresponding to no sensation, 4 corresponding to pain threshold, 7 moderate pain and 10 worst pain imaginable. Participants were trained to rate each stimulus prior to starting the experiment. Once the participants reached a moderately painful level (7 on the pain scale) the laser was stopped, and the energy required to elicit a rating of 7 was recorded. This procedure was repeated a minimum of three times for each arm to ensure that ratings remained reasonably consistent. The level 7 was set independently for each arm. Participants were then asked to rate their level of state anxiety using a 0 to 100 visual analogue scale (VAS) (0 no anxiety - 100 extreme anxiety), this was repeated at each treatment phase and at the end of the experiment.

Pre-experiment questionnaires

Prior to starting the experiment, participants were asked to complete the following questionnaires which were used to assess levels of psychological distress and other psychological variables that predict pain experience: the State-Trait Anxiety Inventory (STAI) [42], the Pain Anxiety Symptoms Scale (PASS) [28], the Hospital Anxiety and Depression Scale (HADS) [57], the Pain Catastrophizing Scale (PCS) [45], the Life Orientation Test (LOT-R) [40] and the Healthy Anxiety Inventory (HAI) [39].

Procedure

The procedure followed a strict script, followed verbatim for both the placebo and control groups: Participants were informed which group they will be in after signing the consent form. Participants in the placebo treatment group were told ‘you may or may not receive a local anaesthetic cream to your right forearm arm’. However, all participants in the placebo treatment group received

an inactive cream on both arms. Whereas participants in the control group were told explicitly that they would receive an inactive cream on both arms. Therefore, the right arm was conditioned within the placebo group and not in the control group. We have previously shown this to be a successful method of inducing placebo conditioning [52,53]. The procedure schematic is represented in Figure 1. In the following, the three experimental phases of the experiment are described as per the placebo (sham-treated) group.

Insert Fig 1 about here

Pre-conditioning phase (Phase 1)

Before application of the cream participants were asked to rate 20 laser stimuli using the NRS 0–10 pain scale - 10 stimuli to the dorsum of the left forearm and 10 stimuli to the dorsum of the right forearm. All pulses were delivered at the individually identified laser energy corresponding to the moderately painful level 7.

Conditioning phase (Phase 2)

Application of sham local anaesthetic (placebo) cream: Aqueous cream, containing paraffin oils was placed on a strip of occlusive, transparent, film dressing (Tegaderm, 3M Healthcare, St Paul, MN, USA). The cream, covered by the dressing, was then placed upon the entire laser stimulation area of both right and left forearms. The occlusive dressing held the cream in position, and this was left in place for 30 min during which time participants were told that the cream would take effect. The appearance of the cream and its application

(using the occlusive dressing), was similar to those commonly used for the local anaesthetic cream EMLA. This was important to reinforce conditioning. Each participant was then asked to rate their expectations regarding pain reduction by indicating on a “Expectation for Pain Relief Scale” using a 0 to 100 VAS (0 = no expectation of pain relief - 100 = high expectation of pain relief) [49]. After 30 min the dressing was removed, and the cream was wiped off.

Following removal of the cream, participants again received 10 laser stimuli to each forearm, but at a surreptitiously reduced energy level just on their right forearm. The reduced energy level corresponded to their individually identified non-painful level 3, while all pulses delivered to the left forearm were still maintained at a laser energy corresponding to the moderately painful level 7. The surreptitious lowering of the laser energy delivered to the right forearm (and not the left forearm) made it easier for participants to compare the sensation directly to their experience of the laser on the other arm. This was a method we had previously used and allowed us to identify site-specific effects vs. non-specific effects that generalise to other regions of the body [52]. This was intended to reinforce the perception that participants had received an active local anaesthetic cream to the right forearm only and that it was having an effect. Participants rated the laser pulses using the 0–10 NRS pain scale. Participants were then asked again to rate their level of anxiety and expectation of pain relief, before entering, almost immediately, into the post-conditioning phase of the experiment.

Post-conditioning phase (Phase 3)

In this post-phase, laser energy applied to the right forearm was surreptitiously raised to the pre-conditioning level, so both arms received laser energy at the participant's original level 7 (perceived to be moderately painful). Participants were asked to rate another 10 pulses on each forearm at this level.

Control group

The intention of the control group was to control for the effects of verbal suggestion on placebo conditioning. Participants in the control group experienced exactly the same procedure in *pre-phase*, *conditioning phase* and *post-phase* as the placebo group, the only difference being was that they were informed throughout the experiment that, i) the cream was inactive and ii) that the laser stimulus would be turned down to a non-painful level just on the right forearm, during the *conditioning phase*. By informing control participants that they were receiving an inactive cream, and that laser energy would be reduced, this controlled for the effects of verbal suggestion, but potentially allowed for unconscious conditioning effects (occurring due to the participants' experience of experimental pain reduction) that matched those of the placebo group.

Reproducibility

A least two weeks after the first session, participants returned for a repeat session. The two sessions are henceforth referred to as Session 1 and Session 2. In Session 2, participants were assigned to the same group and given exactly the same treatment and instructions as in Session 1. To minimise carry-over effects from the first session, all participants were informed that the

treatment they received in the first session would not impact upon the effects of the treatment they received in the second session.

Data analysis

We used linear mixed effects models (LMMs) to test for the presence of placebo effects and to test the hypothesis of group differences in placebo effects. Details of the models used are in Supplementary Materials. The "phase" effect (change in pain ratings from phase 1 to phase 3) was included to test for placebo effects, with "arm" (treated and non-treated) as a separate fixed effect that was expected to interact with phase. We also examined whether there was an effect of session. Analyses adjusted for the potential confounding effect of the pain rating reported during conditioning (phase 2) of the experiment by using the mean pain rating from phase 2 as a participant-level fixed-effect covariate. We also controlled for the laser energy used to elicit pain during the experiment, and participants' age and gender, as fixed effects. Participants were treated as random effects to allow overall pain ratings and placebo effects to vary across participants (see Supplementary Materials for details). Because we used LMMs, we examined the distribution of the residuals of the pain ratings were fitting to the model. Normal probability plots showed that the distribution of the residuals was normal with approximately equal variance over conditions and groups. All statistical tests were 2-sided, with $\alpha = 0.05$. Analyses were performed using both R and Matlab 2019a (MathWorks Inc.) softwares.

Intraclass correlation coefficients (ICCs) were calculated to examine the test–retest reliability of the placebo effects between the two sessions, using

data from the treated arm only. For this calculation we used LMMs to identify variance components for the random effects (participants) and model error term. Further details are in Supplementary Materials.

In addition to investigating placebo effects on pain ratings, we also tested for conditioning-induced changes in anxiety and expectation, primarily focussing on ratings collected both immediately prior and subsequent to conditioning (Anx3 to Anx4, and Exp1 to Exp2 – see Figure 1). Similar LMMs were fitted to this data as per the placebo pain ratings models (model details in Supplementary Materials). We also tested for group differences and trends over time in anxiety ratings over the whole experiment (Anx1 to Anx5). Finally, we tested whether these state variables influenced the response to sham treatment by fitting additional pain rating models that included these state variables (expectation and anxiety) as either main effects or interactions with experiment phase (pre to post-conditioning).

Finally, we investigated whether the conditioning procedure was effective at inducing placebo responses by using LMMs to compare the groups (placebo vs. control) in the extent to which decreases in pain ratings measured during the conditioning procedure predicted decreases in pain ratings in the post-conditioning phase. Importantly, the analysis focussed on site-specific placebo responses by first subtracting mean pain ratings on the untreated arm from those on the treated arm; this also provided control over the confound of habituation effects that might otherwise cause a spurious correlation between conditioning phase and post-conditioning phase pain ratings (caused by different participants habituating at different rates) – since both arms would be

expected to habituate at the same rate. Further details of the models are in Supplementary Materials.

Results

Characteristics of the diagnostic groups

237 participants completed the study (60 OA, 79 FM and 98 HI). A summary of characteristics is shown in Table 1.

Insert Table 1 about here

Laser energy

The energy levels required to elicit a moderately painful subjective level 7 rating were similar between OA and HI groups (HI=17.85±3.1 mj/mm^2, OA=18.8±3.36 mj/mm^2, p=0.06), but significantly lower in FM participants (FM=16.2±4 mj/mm^2, HI vs FM p<0.001, OA vs FM p<0.001). Hence, these values were included as a nuisance covariate in statistical analyses of placebo effects.

Psychometric tests

One-way ANOVA on the diagnostic groups showed a highly significant effect of diagnosis on certain psychological variables that had previously been shown to predict pain experience (p<0.001; Table 2), with OA, FM and HI groups all showing significantly different outcomes. Post-hoc data indicated that FM patients reported significantly increased levels of psychological distress than their OA and HI counterparts in almost all examined outcomes, except in

pain anxiety symptoms where FM and OA displayed similar outcomes (PASS avoidance, p=1; PASS fearful thinking p=0.074).

Insert Table 2 about here

The placebo effect

There was a placebo effect evident from a significant 2-way interaction between treatment group and phase of the experiment, indicating that pain ratings were more decreased, on average, by 0.74 (out of 10 on the numerical rating scale) from pre to post-conditioning in the placebo treatment group compared to the control group ($t = -5.14$, $p < 0.001$, 95% CIs: -0.99 to -0.50, Table 3). Additional but weaker variance in pain ratings was accounted for by a 3-way interaction between treatment group (placebo treatment vs. control), phase of the experiment (pre vs. post conditioning) and arm (treated vs. untreated). This interaction indicated that pain ratings changed (with the negative sign indicating a decrease) on average by a further -0.26 points ($t = -3.14$, $p = 0.002$, 95% CIs: -0.10 to -0.43, Table 3) due to the additional effect of the treated vs. untreated arm. Overall, this indicates a placebo effect that is evident on both arms (treated and untreated) but is larger on the treated arm. These effects are plotted as fitted group means and CIs of the mean in Figure 2. A Likelihood Ratio Test provides strong support for a model of the pain ratings that includes these interactions compared to a control model without these interactions ($LR = 152.6$, $p<0.001$; comparison of model 2 vs. model 1 in Supplementary Materials).

Insert Table 3 and Figure 2 about here

Although, on average, there was a significant placebo effect, there was considerable variation between participants, evident from the random effect coefficients. The random effect (i.e. participants) for the phase slope (change from pre to post-conditioning) in the model, indicating individual variability in the magnitude of the placebo response, had a standard deviation of 0.89 (95% CIs: 0.80 to 0.98) points on the 0-10 rating scale, even after accounting for the fixed effect of treatment group in the model. This indicates a considerable variability between participants in the placebo response within the treatment and control groups.

However, we did not find evidence that the placebo effect varies significantly across diagnostic groups (OA, FM, HI). Firstly, a Likelihood Ratio Test did not favour strongly enough a model in which diagnostic group interacted with the factors of treatment group, experiment phase, and arm treated ($LR = 23.2$, $p = 0.06$). Secondly, results from the model including these interaction terms involving diagnostic group did not reveal any significant interactions. Violin plots (Figure 3) show that all three diagnostic groups who were treated with placebo (i.e. sham treatment groups) showed lower levels of reported pain following application of the placebo cream compared to their control group counterparts, and this was the case in both sessions.

Insert figure 3 about here

Test-retest reliability of the placebo effect

We tested a further mixed model (model 4 – see Supplementary Materials) in which interaction terms were added involving the factor Session. A Likelihood Ratio Test found that this did not improve model fit, suggesting that placebo effects were not depending on the experimental session. To formally investigate test-retest reliability of the placebo effect over sessions, intra-cluster correlation coefficients (ICCs) were calculated on mean pain ratings post-conditioning, after adjusting for pre-conditioning mean pain ratings. The ICC for the sham treatment groups was 0.77, indicating moderately good test-retest reliability, while for the control groups the ICC was weak at 0.21. Breaking down the ICC for the treatment groups into diagnostic sub-groups, the ICCs for the OA, FM and HC groups were 0.78, 0.80 and 0.72 respectively. To visualise the relative difference in placebo effects from session 1 to session 2, Figure 3 plots lines indicating the placebo effect across sessions, for each participant.

Expectation of pain relief

Expectation of pain relief was reported by participants twice during the experiment (pre and post cream application), and the change in expectation ratings was analysed (Exp1-Exp2). There was a clear effect of placebo treatment ($p<0.001$, Figure 4, Table 4), however no effect of session or diagnosis.

Insert Table 4 and Figure 4 about here

Anxiety

Anxiety levels were measured at 5 time-points (Anx1 to Anx5, Table 5) throughout the experiment. There was a clear effect of diagnosis on anxiety ($F=27.47$, $p<0.001$, Figure 4), with FM patients rating higher anxiety levels than both OA and HC participants throughout the experiment (Figure 5). There was also a significant linear trend over time in anxiety ratings from Anx1 to Anx5 ($F=16.98$, $p<0.001$) and anxiety ratings were overall lower in session 2 compared to session 1 ($F=10.55$, $p=0.001$). However, after adjusting for pre-treatment anxiety levels, there was no indication that changes in anxiety during the conditioning phase (i.e. change in anxiety levels between time-points Anx3 and Anx4) were specifically influenced by diagnosis, treatment or session (Figure 4, Table 4).

Placebo effect – Independent of expectation and anxiety

The placebo effect did not appear to be predicted by, or mediated by, expectation or anxiety. Specifically, we found that adjusting for either the baseline levels, or for the pre-post conditioning changes, in expectation or anxiety within the model of placebo effects did not remove the placebo effect. Likelihood Ratio Tests did not favour models that included these variables as either main effects or interacting with terms in the model that included phase (pre vs. post treatment).

Insert Table 5 and Figure 5 about here

Differential prediction of the placebo response by conditioning responses in placebo and control groups

Additional linear mixed models tested for the prediction of site-specific placebo responses (defined by relatively greater decreases in mean pain ratings on the treated vs. untreated arm) from the reductions in pain experience during conditioning (see models 9 to 11 in Supplementary Materials). We initially tested (model 9) whether the linear relationship between conditioning decreases in pain and placebo responses differed between the placebo and control groups. The rationale is that since the control group went through the same conditioning procedure as the placebo group, but were informed that the cream was not an analgesic, this analysis provides further insight into the role of conscious expectation in the efficacy of the conditioning procedure. Specifically, if conditioning required only unconscious processes, the relationship between conditioned and placebo responses would be expected not to differ between groups. However, we found that there was a statistically significant interaction between the fixed effect of group and the conditioning phase decrease in pain in the model (beta = 0.12, 95% CIs: 0.02 to 0.22, t = 2.27, p = 0.024, Table 6). To explore this further, two separate models (models 10 and 11) were conducted as follow-up tests, showing that the conditioning-related decreases in pain significantly predicted the placebo response only in the treated group (beta = 0.20, 95% CIs: 0.13 to 0.27, t = 5.93, p < 0.001, Table 6) but not in the control group (beta = 0.05, 95% CIs: -0.03 to 0.12, t = 1.18, p = 0.241, Table 6). For illustration purposes, the relationships are plotted in Figure 6 using only the data from session 1 (for which there is the largest sample of data). Overall, the results show that the placebo response can be explained by the impact of the conditioning procedure only in the placebo group,

suggesting that the effect of conditioning on the placebo effect depends upon congruent expectations (of pain relief) that were only present in that group.

Insert Table 6 and Figure 6 about here

Discussion

We investigated the reproducibility of placebo analgesia across patients with OA and FM, as well as pain-free HI. We also studied whether expectation of pain relief, psychological distress and changes in anxiety during the procedure were predictors of placebo responses. Lastly, we tested whether placebo responses could be predicted from decreases in pain during conditioning. We found that despite psychological co-morbidities, patients with OA and FM displayed similar experimental placebo analgesic responses to their HI counterparts. This included similar levels of reproducibility and expectations of pain relief. While findings suggested that the placebo response is not predicted or mediated by participants' judgements of their changes in expectation or anxiety, we did find that it was only in the placebo group (who had a conscious expectation of pain relief) that there was a relationship between conditioning and post-conditioning reductions in pain, suggesting that the placebo effect depends upon congruent expectations of pain relief.

Previous evidence for the efficacy and reproducibility of placebo analgesia mainly exists from experimentally evoked pain studies in healthy individuals [2,9,14,51,52,54]. Whereas, evidence for positive placebo analgesic responses and reproducibility in individuals with chronic pain primarily comes from the placebo arm of pharmacological randomised controlled trials

[8,20,21,56]. Here we have shown that placebo responses to experimentally induced pain are as equally reproducible in individuals with chronic pain, as in healthy individuals. As far as we are aware, this is the first study to compare responses between these groups within the same study.

Placebo responders and the placebo response have been previously linked to cognitive traits, such as lower levels of state anxiety [31] and reduced negative emotional processing [3,35]. In contrast, the psychological co-morbidities associated with chronic pain conditions, such as depression and anxiety, have been implicated in reducing the effectiveness of placebo analgesia in chronic pain patients [33,30,46]. Based on this, we anticipated that OA and FM patients would exhibit a reduced placebo response compared to their HI counterparts, but in our study this was not the case.

Correlations between changes in expectation with the magnitude of placebo analgesia have previously been observed [34,36]. This is thought to occur because sensory experiences such as pain are influenced by the interaction between expectations (e.g. of pain relief) and sensory information, such as nociception. Because expectancy is believed to play a significant role in initiating placebo effects, individual differences in placebo analgesia may also be driven by differences in expectancy. Where placebo responses are large for a particular individual or situation, this can be seen as a triumph of expectation over current sensory information [32]. Interestingly, while participant ratings of expectation or anxiety did not predict placebo responses, there was only a relationship between conditioning phase and post-conditioned reductions in pain ratings in the placebo group. This is consistent with the view of previous researchers that conscious expectations may interact with

unconscious conditioning processes for placebo effects to be realised [44]. Insight on the discrepancy between these two analyses comes from recent debate about the role of predictive coding schemes in the brain [7] in which prior experiences (e.g. conditioning) may generate 'unconscious predictions'. If partially unconscious, participants may not accurately report on their expectations but may nevertheless by influenced in their perception and reporting of pain. This may also account for the placebo response observed on the untreated arm in our study: our results showed a placebo effect on both arms, which to a degree makes it a non-specific effect, although with a larger effect seen on the treated arm. In other words, our data suggests we have seen both arm-specific, as well as arm non-specific effects, which is one of the novel findings of this study.

Consistent with our observation of equivalent placebo responses between diagnostic groups, expectation of pain relief, and relative increases in expectation through conditioning, were also similar across diagnostic groups and healthy controls. This suggests that, despite living with chronic pain, individuals with OA and FM still have normal expectancy of pain relief, as well as normal updating of expectancy by conditioning. This is of interest because, although it was not assessed in our study, individuals with chronic pain are more likely to have numerous (positive or negative) healthcare experiences compared to healthy individuals [13], which could affect the expectation of pain relief in future treatments [17]. With our chronic pain cohort, their history of pain, previous treatment experiences, and the refinement of their expectations and beliefs that may result from those experiences, did not appear to interfere with the efficacy of their placebo response.

We also examined anxiety levels during the placebo/sham and control procedures. Unlike expectations of pain relief, we saw a significant difference in baseline levels of anxiety between diagnostic groups. This is consistent with the known psychological comorbidities often experienced by patients with chronic pain, including anxiety and depression [11], pain catastrophizing [19] and cognitive impairments [7,18]. While previous studies suggest that psychological symptomatology can predict the magnitude of the placebo response, but our findings have been contradictory. Wasan et al. found that high levels of psychopathology, including pain-related anxiety, are associated with *heightened* placebo analgesia in chronic lower back pain patients [49], while Lyby showed that increased levels of stress and fear of pain *reduces* the placebo analgesic response in healthy participants [27]. We have previously reported that low state anxiety is a significant predictor of placebo response in healthy individuals [33]. Contrary to these findings, our current data shows that although anxiety levels between diagnostic groups varied significantly, the placebo response did not. Although FM patients showed higher levels of anxiety than both OA and HI participants throughout the experiment, the FM placebo response was no different. The disparity to previous literature could be due to differences in the way participants were selected, differences in the methods used to assess psychological variables (we assessed anxiety whereas Lyby assessed fear of pain and stress), or differences in the placebo paradigm (e.g. our study used conditioning and Wasan's study did not) [49,27].

Throughout our experiment we observed a significant linear trend in the reduction of anxiety in all diagnostic groups over time (highlighted in Figure 5). Anxiety levels further reduced in Session 2. Lu et al. also reported similar

reductions in anxiety levels in IBS patients [26], but our study is the first, of which we are aware, that observes equivalent changes in anxiety in OA and FM patients. It is also of interest to note that any decrease in anxiety was not specific to the placebo treatment, as it was also evident in the untreated control groups. Previous research has also failed to elucidate a clear and consistent relationship between changes in anxiety and placebo analgesia. Some evidence suggests changes in anxiety might contribute to the placebo analgesic response [12], while other evidence suggests placebo analgesia is the causal factor in a reduction in state anxiety [25]. While the mechanistic contribution of changes in anxiety are unclear, our results do indicate that changes in anxiety are not dependent on initial levels of anxiety, a finding that has not been previously reported.

A limitation of our study is the possibility of selection bias that might limit generalisation of the findings. Specifically, a meaningful proportion of patients in our study were recruited from the same rheumatology clinic, which means our results apply to a specific demographic. For instance, patients from the same area may have had similar healthcare experiences, which has been shown to alter expectations [17].

Regarding clinical implications, our results suggest that individuals with FM and OA can modulate their responses to experimental pain as efficiently as healthy individuals. In this context, given equally efficient endogenous analgesia across diagnostic groups, our findings suggest potential for the exploration of new treatment strategies that enhance the placebo response, or otherwise utilise endogenous analgesia in these patients, in order to improve treatment outcomes.

The finding that experimental placebo responses in both OA and FM groups were reproducible has some potentially important implications for clinical trial design. The variability of placebo response between individuals is a major problem, particularly for early or small clinical trials of analgesics [12]. One approach to this has been to exclude placebo responders during a pre-screening process (run-in trials) [25]. However, this results in conducting trials on non-representative populations of patients. An alternative strategy is to balance the number of placebo responders in each arm using an experimental placebo procedure to screen for responders/non-responders. However, the validity of the screening procedure depends on how reproducible the placebo response is. Our results show that experimental placebo analgesia is sufficiently reproducible to justify exploring these approaches for balancing placebo responders across arms of a clinical trial.

In summary, by using standardised method for inducing placebo analgesia, we found similarly reproducible changes in expectancy, anxiety and pain experience, as a result of experimental placebo, in individuals with OA and FM compared to pain-free healthy volunteers. Treatment approaches seeking to maximise placebo analgesia may therefore have equal chance of success in both OA and FM populations.

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Conflicts of interest

The authors declare no conflict of interest, including competing financial interests.

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Figures

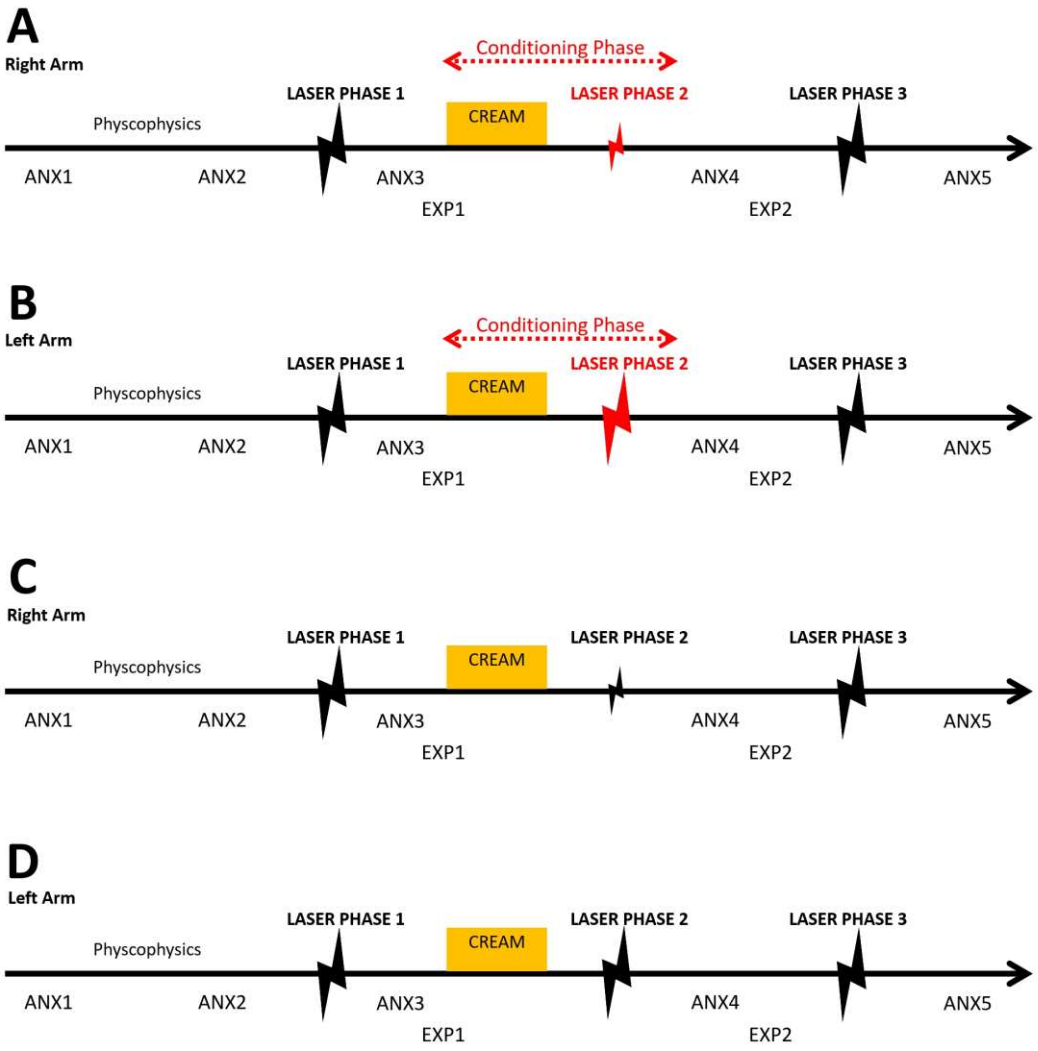

Figure 1: Study design over time showing the various points at which participants rated laser intensity (Laser Phase 1-3), anxiety levels (ANX1-5) and expectation of pain relief (EXP1-2). The difference between the experimental groups [placebo treated arm (A), placebo untreated arm (B), control treated arm (C), control untreated arm (D)], depended on how the laser energy in phase 2 was manipulated. In all cases inert aqueous cream was applied to both forearms. In the placebo group the right forearm was conditioned to associate the cream with pain reduction by surreptitiously reducing the laser energy level (A), while the left forearm received the painful

laser energy (B). The control group were told explicitly that the cream was inert and that the laser energy would be reduced on their right forearm (C), thereby eliminating the effects of conditioning, while their left forearm received the painful laser energy (D). Laser pulses lasted 150 ms, with a beam diameter of 15 mm. Energy levels required to elicit a level 7 response on the pain rating scale ranged between 6.1 and 27.6 mj/mm^2.

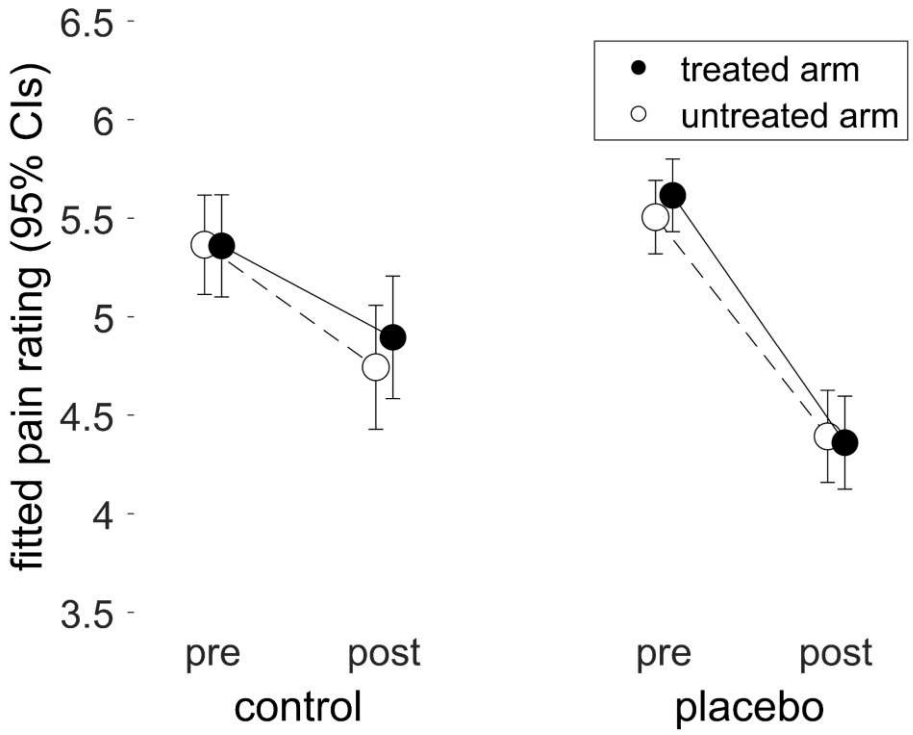

Figure 2. Plot showing a change in pain rating due to the interaction between treatment (placebo vs control), phase (pre vs post conditioning phase) and arm (treated vs. untreated). Here we see a clear placebo effect on both arms (treated and untreated) which is greater on the treated arm which received conditioning. Circles are fitted values and error bars are 95% confidence intervals

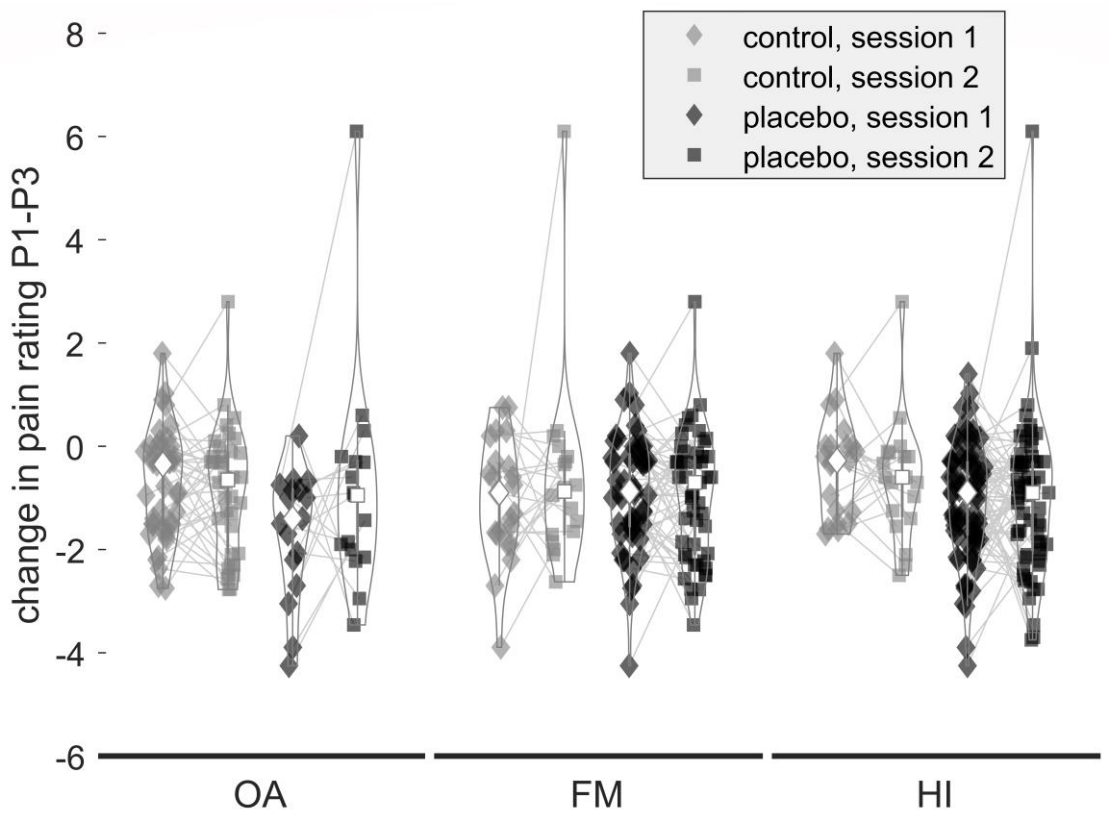

Figure 3. Violin plots of subject means change in pain rating (phase subtracted P1-P3, arm 1 only) shows reduced levels of reported pain in the placebo group following cream application than in the control group. This effect was reproducible in both sessions. Group, treatment and session effects are displayed as violins, with session 1 & 2 paired with lines. A perfectly horizontal line for a participant would indicate the same magnitude of placebo response; a slope to the line indicates a change in magnitude. OA = osteoarthrosis, FM = fibromyalgia and HI = healthy individual groups.

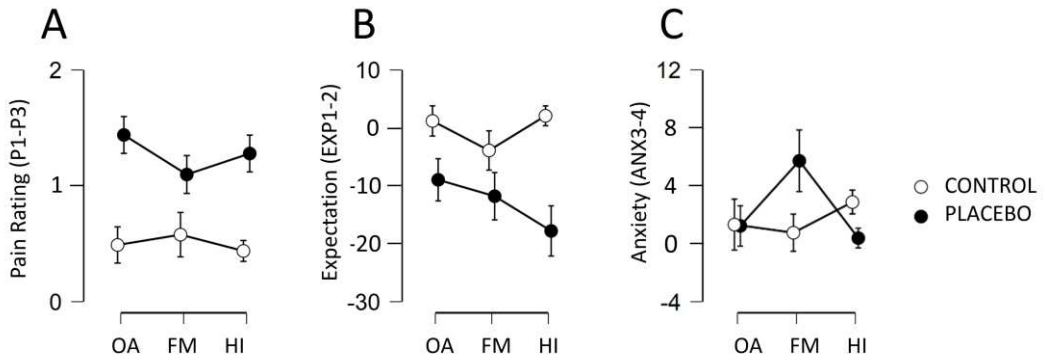

Figure 4. Descriptive plots showing change in pain (A), expectation (B) and anxiety (C) following the placebo and control cream in osteoarthrosis (OA), fibromyalgia (FM) and healthy (HI) groups. A. Change in Pain Rating between Phases P1 and P3 shows greater changes in pain across all diagnostic groups following the placebo opposed to the control treatment. (B) Change in Expectation of Pain Relief between EXP1 and EXP2 shows an increased change in expectation following placebo treatment. Here lower values indicate a greater increase in change and (C) the Change in Anxiety Rating between ANX3 and ANX4 time-points shows no difference between Placebo and Control treatment groups. Error bars indicate SEM.

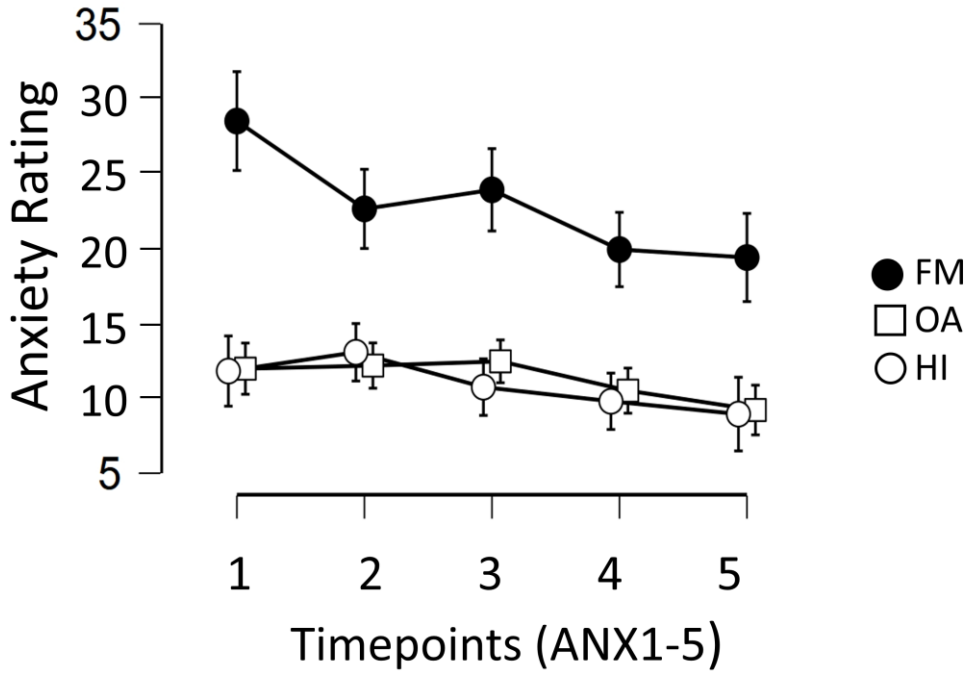

Figure 5. A descriptive plot showing reported VAS anxiety levels at 5 time-points, ANX1-5, during the experiment. Osteoarthrosis patients (OA) and healthy individuals (HI) reported similar levels of anxiety at all 5 time-points during the experiment, while fibromyalgia (FM) patients rated significantly higher anxiety levels throughout. Error bars indicate SEM.

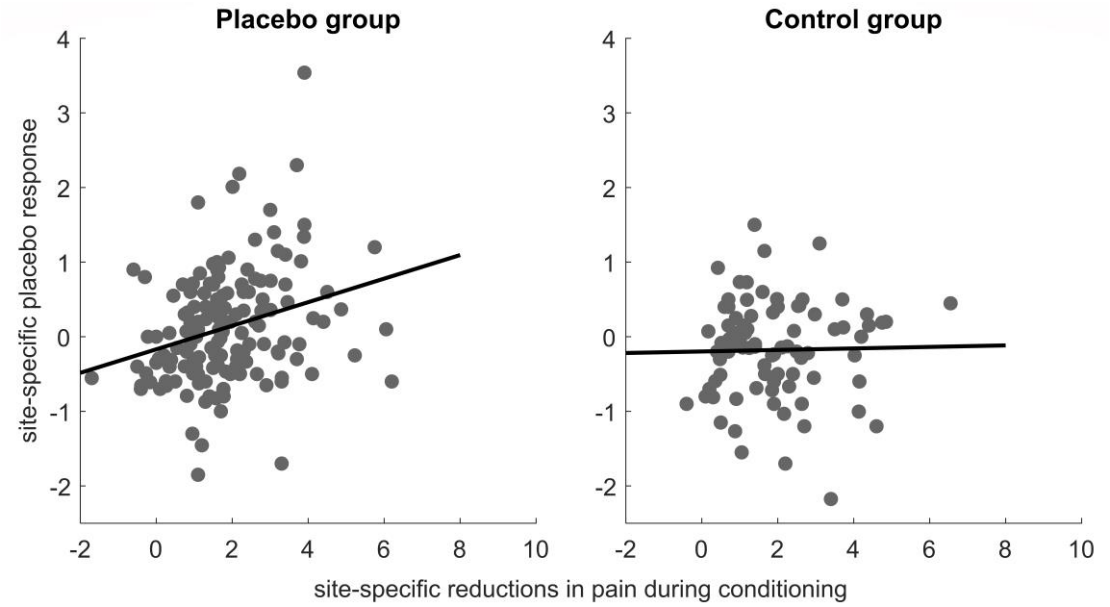

Figure 6. Scatter plots (with least-squares lines) showing site-specific decreases in pain from the conditioning phase as a predictor of the site-specific placebo response in each group (placebo and control). The site-specific placebo response is calculated here as the mean pain ratings (for the treated arm minus the untreated arm) in the post-conditioning phase minus the pre-conditioning phase (P3-P1). Similarly, the site-specific decrease in pain during conditioning is calculated as the mean pain ratings (for the treated arm minus the untreated arm) in the conditioning phase minus the pre-conditioning phase (P2-P1). A significant prediction is only observed in the placebo group (for statistics, see models 10 and 11 in Table 6).

Table 1: Characteristics of the osteoarthritis (OA), fibromyalgia (FM) and pain-free healthy (HI) participants. Participants were assigned into Placebo and Control groups. N: numbers of participants in each group. SEM: Standard Error of the Mean.

Characteristic	**Control Group (n = 87)**			**Placebo/Sham Treatment Group (n = 150)**		
	N (%) of control group)	Age (yrs ± SEM)	N (%) females	N (%) of placebo group)	Age (yrs ± SEM)	N (%) females
OA	22 (25%)	58.8±1.47	9 (39%)	38 (25%)	60.9±1.8	18 (47%)
FM	24 (28%)	50.9±1.9	20 (83%)	55 (37%)	51.3±1.37	48 (87%)
HI	41 (47%)	34.8±1.76	27 (66%)	57 (38%)	38.3±1.59	32 (56%)
Age (yrs ± SEM)	46±1.6			49±1.2		
N (%) females	56 (64%)			98 (65%)		

Table 2: One-way ANOVAs on the diagnostic groups for psychometric measures.

Questionnaire	OA	FM	HI	ANOVA (p-value)	Post hoc (p-value)		
					OA vs FM	OA vs HI	FM vs HI
STAI2	29.25 ±0.13	38.59± 0.13	27.94± 0.07	p<0.001**	p<0.001**	p=0.948	p<0.001**
STAI1	30.24 ±0.19	39.29± 0.14	27.92± 0.08	p<0.001**	p<0.001**	p=0.391	p<0.001**
STAI1V2	28.31±0. 14	38.44± 0.19	27.37± 0.09	p<0.001**	p<0.001**	p=1.000	p<0.001**
HADS Anxiety	5.66 ±0.06	10.5±0 .06	5± 0.036	p<0.001**	p<0.001**	p=0.889	p<0.001**
HADS Depression	3.96 ±0.062	9.37±0 .06	2.57±0 .027	p<0.001**	p<0.001**	p=0.055	p<0.001**
HAI	12.34±0. 12	19.5±0 .126	9.56±0 .06	p<0.001**	p<0.001**	p=0.071	p<0.001**
LOTR V1	14.0±0.0 7	11.23± 0.07	14.68± 0.05	p<0.001**	p=0.002*	p=1.000	p<0.001**
LOTR V2	14.8 ±0.08	12.39± 0.06	15.75± 0.05	p<0.001**	p=0.007*	p=0.620	p<0.001**
PCS Rumination	5.304±0. 06	8.014± 0.07	4.022± 0.04	p<0.001**	p<0.001**	p=0.190	p<0.001**
PCS Magnification	2.339±0. 03	4.181± 0.05	1.699± 0.02	p<0.001**	p<0.001**	p=0.392	p<0.001**
PCS Helplessness	5.732±0. 07	11.27± 0.09	3.473± 0.04	p<0.001**	p<0.001**	p=0.0024*	p<0.001**
PASS Avoidance	10.77±0. 10	11.51± 0.08	7.389± 0.06	p<0.001**	p=1.000	p<0.001**	p<0.001**
PASS fearful thinking	5.196±0. 09	7.11±0 .08	3.1±0. 04	p<0.001**	p=0.074	p=0.029*	p<0.001**
PASS cognitive anxiety	9.21±0.0 99	14.24± 0.08	7.09±0 .06	p<0.001**	p<0.001**	p=0.070	p<0.001**
PASS physiological response	4.43±0.0 7	9.04±0 .08	4.01±0 .05	p<0.001**	p<0.001**	p=1.000	p<0.001**

Mean ± SEM. Bonferroni post hoc tests highlight differences and similarities between the diagnostic groups.
STAI, State-Trait Anxiety Inventory; HADS, Hospital Anxiety and Depression Scale; HAI, Healthy Anxiety Inventory; LOT-R, Life Orientation Test; PCS, Pain Catastrophizing Scale; PASS, Pain Anxiety Symptoms Scale.
Significance at the 95% level, *p<0.05, **p<0.001.

Table 3: Fixed effects from Model 2 (for models, see Supplementary Materials), including interactions between treatment (placebo vs control), phase (pre vs post conditioning phase) and arm (treated vs. untreated) to test for the presence of a placebo effect. Beta coefficients are unstandardized and categorical predictor variables are dummy coded, such that beta coefficients are interpretable in terms of the original 0-10 pain scale (e.g. a beta value of 1 indicates a change of 1 on the pain scale). Significance at the 95% level, *p<0.05, **p<0.001, ***p<0.0001

	Coefficients						**ANOVA contrasts**			
Parameter	**beta**	**SE**	**t**	**p value**	**CI-95%, lower**	**CI-95%, upper**	**F**	**DF1**	**DF2**	**p value**
(Intercept)	5.60	0.46	12.25	p<0.0001***	4.70	6.49	150.17	1	23882	p<0.0001***
group	-0.10	0.16	-0.61	p=0.544	-0.41	0.22	0.96	2	23882	p=0.358
	-0.25	0.18	-1.37	p=0.171	-0.61	0.11				
treat	0.25	0.13	1.89	p=0.059	-0.01	0.51	3.56	1	23882	p=0.059
session	0.02	0.11	0.17	p=0.866	-0.19	0.23	0.03	1	23882	p=0.084
phase	-0.49	0.10	-4.83	p<0.0001***	-0.69	-0.29	23.37	1	23882	p<0.0001***
arm	0.48	0.06	7.39	p<0.0001***	0.61	0.35	54.67	1	23882	p<0.0001***
age	-0.02	0.01	-2.90	p=0.004*	-0.03	0.00	8.39	1	23882	p=0.0038*
gender	-0.13	0.13	-1.03	p=0.304	-0.37	0.12	1.06	1	23882	p=0.304
laser energy	-0.18	0.17	-1.08	p=0.278	-0.50	0.14	1.18	1	23882	p=0.278
phase2_mean	0.25	0.01	18.15	p<0.0001***	0.22	0.28	329.33	1	23882	p<0.0001**
treat:phase	-0.74	0.13	-5.86	p=0.0002**	-0.99	-0.49	34.36	1	23882	p=0.0001***
treat:arm	0.09	0.07	1.24	p=0.217	0.24	-0.05	1.53	1	23882	p=0.207
phase:arm	0.14	0.07	-2.14	p=0.032*	0.27	0.01	4.58	1	23882	p=0.032*
treat:phase:arm	-0.26	0.08	-3.07	p=0.002*	-0.09	-0.42	9.43	1	23882	p=0.002*

Table 4. Factorial (two-way) ANOVAs with factors for Treatment (Placebo group, Control group) and Diagnosis (fibromyalgia, osteoarthritis, and healthy). 3 ANOVAs were conducted, on Change in Expectation of pain relief, Change in Anxiety, and the subsequent Change in Pain rating (after the conditioning procedure).

	Change in Expectation	Change in Anxiety	Change in Pain
Treatment	F=17.059; p<0.001**	F=0.385; p=0.536	F=31.74; p<0.001**
Diagnosis	F=0.70; p=0.498	F=0.826; p=0.44	F=0.296; p=0.744
Treatment x Diagnosis	F=1.503; p=0.226	F=3.06; p=0.049*	F=0.819; p=0.442

Significance at the 95% level, *p<0.05, **p<0.001, ***p<0.0001

Table 5. VAS Anxiety levels measured at 5 time-points (Anx1-Anx5) throughout the experiment. Osteoarthrosis (OA), fibromyalgia (FM) and healthy (HI) groups.

Anxiety Rating	OA	FM	HI	P value	F values	df
Anx1	12.17±15.83	28.481±24.82	12±14.87	p<0.0001***	19.36	2,30
Anx2	12.69±12.62	22.86±19.93	12.29±13.03	p<0.0001***	11.39	2,27
Anx3	10.19±12.41	24.01±20.90	12.26±12.33	p<0.0001***	16.69	2,29
Anx4	9.53±12.34	20.62±19.34	10.38±12.89	p<0.0001***	12.45	2,29
Anx5	8.84±16.04	19.05±22.25	9.29±14.1	p=0.0003**	8.24	2,31

Significance at the 95% level, *p<0.05, **p<0.001, ***p<0.0001

Table 6: Effect of pain reductions during the conditioning phase ("conditioned" in the table) on placebo responses. Results are from the linear mixed models 9 to 11 in Supplementary Materials, which controlled for pre-conditioned pain ratings and session. Placebo and conditioning changes are site-specific (i.e. mean pain ratings from the treated arm minus the untreated arm), which also controls for habituation effects over time. Beta coefficients are unstandardized and the categorical predictor variable (group: placebo vs. control) are dummy coded.

Interaction between group and conditioned responses (model 9)						
Parameter	**beta**	**SE**	**t**	**p value**	**CI-95%, lower**	**CI-95%, upper**
(Intercept)	-0.29	0.10	-2.85	p=0.005*	-0.50	-0.09
conditioned	0.07	0.04	1.74	p=0.082	-0.01	0.15
treat	0.04	0.12	0.34	p=0.735	-0.20	0.28
treat:conditioned	0.12	0.05	2.27	p=0.024*	0.02	0.22
session	-0.01	0.07	-0.18	p=0.858	-0.15	0.13
pre-conditioned	0.74	0.06	13.14	p<0.0001***	0.63	0.85
Conditioned responses in the placebo group (model 10)						
Parameter	**beta**	**SE**	**t**	**p value**	**CI-95%, lower**	**CI-95%, upper**
(Intercept)	-0.27	0.09	-3.05	p=0.0025*	-0.44	-0.09
conditioned	0.20	0.03	5.93	p<0.0001***	0.13	0.27
session	-0.05	0.09	-0.56	p=0.573	-0.23	0.13
pre-conditioned	0.64	0.07	8.69	p<0.0001***	0.49	0.78
Conditioned responses in the control group (model 11)						
Parameter	**beta**	**SE**	**t**	**p**	**CI-95%, lower**	**CI-95%, upper**
(Intercept)	-0.26	0.10	-2.57	p=0.011*	-0.47	-0.06
conditioned	0.05	0.04	1.18	p=0.241	-0.03	0.12
session	0.03	0.11	0.28	p=0.776	-0.19	0.25
pre-conditioned	0.94	0.08	11.07	p<0.0001***	0.77	1.10

Significance at the 95% level, *p<0.05, **p<0.001, ***p<0.0001