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Meditation experience predicts less negative appraisal of pain: Electrophysiological evidence for the involvement of anticipatory neural responses

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ABSTRACT

The aim of mindfulness meditation is to develop present-focused, non-judgmental, attention. Therefore, experience in meditation should be associated with less anticipation and negative appraisal of pain. In this study we compared a group of individuals with meditation experience to a control group to test whether any differences in the affective appraisal of pain could be explained by lower anticipatory neural processing. Anticipatory and pain-evoked ERPs and reported pain unpleasantness were recorded in response to laser stimuli of matched subjective intensity between the two groups. ERP data were analysed after source estimation with LORETA. No group effects were found on the laser energies used to induce pain. More experienced meditators perceived the pain as less unpleasant relative to controls, with meditation experience correlating inversely with unpleasantness ratings. ERP source data for anticipation showed that in meditators, lower activity in midcingulate cortex relative to controls was related to the lower unpleasantness ratings, and was predicted by lifetime meditation experience. Meditators also reversed the normal positive correlation between medial prefrontal cortical activity and pain unpleasantness during anticipation. Meditation was also associated with lower activity in S2 and insula during the pain-evoked response, although the experiment could not disambiguate this activity from the preceding anticipation response. Our data is consistent with the hypothesis that meditation reduces the anticipation and negative appraisal of pain, but effects on pain-evoked activity are less clear and may originate from preceding anticipatory activity. Further work is required to directly test the causal relationship between meditation, pain anticipation, and pain experience.

1. Introduction

The use of alternative medicine is common for self-managing chronic and stress-related conditions that do not respond well to conventional medicine [15]. Despite this there is debate about whether alternative therapies have anything to offer beyond the placebo effect [24]. A major problem facing research into alternative therapies is the lack of clear hypotheses regarding their therapeutic mechanisms.

One of the few alternative therapies that has been adopted by conventional psychological medicine is mindfulness meditation [22,39,43]. The therapeutic mechanisms of meditation have been discussed in terms of attentional functioning [5,27]. Such mechanisms may be clinically relevant to a wide range of psychological, psychosomatic and stress-related diseases [1,22]. Although there is a broad range of meditation techniques, those related to mindfulness meditation involve training in cognitive control, specifically the ability to voluntarily direct attention to a chosen sensory or cognitive event whilst minimizing distraction by other sensory or cognitive phenomena [27]. Mindfulness methods include focusing on the internal feeling of breathing and other body sensations at objects of concentration.

It has been noted that one aspect of training in meditation is to learn how to re-focus attention away from either past or anticipated future experience and onto present-moment experience [5,10]. Meditation should therefore reduce the emotional appraisal of pain or other stressful events by withdrawing attention away from anticipating their unpleasantness. This would be expected to be associated with reductions in brain processes related to anticipating the unpleasantness of pain, without necessarily reducing those brain processes related to the pain itself.

Research using fMRI suggests that regions of the pain matrix showing differential responses to pain in meditators include the thalamus, primary and secondary somatosensory cortices, insula, prefrontal cortex, and the anterior cingulate cortex [23,34]. However, the effects of meditation may occur at multiple time points in the sequence of anticipating and experiencing pain. Limitations in the design of fMRI investigations have meant that it is not clear whether meditation primarily affects anticipatory or pain-evoked responses. We aimed to resolve this problem using high-density

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electrophysiology to measure affective processing during the anticipation and response to pain.

We recruited participants with a broad range of experience of meditation to compare with a non-meditating control group and to determine the effects of lifetime meditation experience. We hypothesized that meditation experience would be related to anticipatory activity in brain regions such as cingulate, prefrontal and parietal cortices. We used a methodology previously reported [7–9,11] for defining the sources of brain activity during different time periods of anticipation and pain experience. We and others have previously suggested that early anticipatory processes are likely to involve establishing an expectation [8] and confidence in that expectation [9]. However, late anticipatory processes more likely relate to preparatory (e.g. attentional and motor) and motivational processes, as well as establishing top-down influences on pain [8]. It is during late anticipation that we would expect differences in cognitive control to influence the affective appraisal of pain and top-down affective influences on pain perception.

2. Methods

2.1. Participants

The research study was approved by Tameside and Glossop Local Research Ethics Committee. The recruitment of subjects for the study was advertised as open to volunteers both with and without experience of practicing meditation. Our intention was to be as inclusive as possible regarding recruitment of subjects with different types of meditation practice, as long as they declared that "sustained focused attention" was the predominant aspect of their practice, as a way of standardizing their meditation experience.

In total, 27 healthy, right-handed subjects participated in the study (13 female, 14 male; mean age 34 ± 14). All subjects gave informed written consent. Of these subjects, 12 declared having experience of meditation (6 female, 6 male; mean age 37 ± 13), whilst the remaining 15 subjects had no experience of meditation (8 female, 7 male; mean age 32 ± 14). These two groups are referred to as the meditation and control groups respectively. Independent-samples *t*-test statistics revealed no significant difference between the ages of the two groups.

2.2. Measurement of meditation experience

Subjects in the meditation group were questioned about the type of meditation practice they do in terms of (1) which precise method they follow, (2) how long they had been practicing over their whole lifetime, and (3) roughly how many hours per week they currently commit to a formal meditation practice. However, many subjects in the meditation group, in addition to reporting regular formal periods of meditation practice, also reported informal meditation practice during their daily activities, and stated that it was not possible for them to accurately estimate how much time they spend practicing informally each week. Furthermore, many subjects also reported that the number of hours they practice each week has changed since they first began, and could not accurately estimate past meditation experience. From the majority of participants, we therefore did not collect data on the number of hours each week they had practiced in the past.

From this data, we sought to calculate the level of experience of each practitioner to correlate with our experimental data. We regarded the number of hours spent formally practicing each week as an unreliable measure of past experience due to the difficulties in measurement stated above, and chose to calculate meditation experience as the total number of weeks practicing meditation over the whole lifetime of each individual. There were likely to be large differences between participants in the amount of time they have spent each week in formal meditation practice; however a measure based on total weeks of practice had the advantage that we were able to avoid making assumptions which are difficult to justify in the present study design. These assumptions are: (1) that formal meditation practice is the only opportunity that a participant has each day to cultivate mindfulness in their daily life, and (2) that formal meditation practice would be the greatest contributor to variation in the experimental data. In our subject sample it is likely that cumulative *in*formal meditation practice in relation to life experience outside of formal practice is a major contributor to the person's mindfulness skills. This becomes critically important when considering that participants in the present study received no instructions to engage in formal meditation practice during data collection. Hence our experimental results are likely to be more closely related to informal meditation practice, which is nearly impossible to quantify in hours.

Details of the meditation practices reported by the 12 subjects in the meditation group were as follows, and summarized in Table 1. Of the 12, five subjects practiced mindfulness meditation, and reported sustained focus on breathing as their central method. Two subjects practiced Samatha, a Buddhist form of meditation that also uses the breath as a focus. Two subjects practiced Tantra-Yoga (non-Buddhist) which involves visualization and repetition of a personal mantra in time with the breathing. Two subjects practiced Zen (Buddhist) meditation which involved some focus on breathing and body sensations as a whole. The remaining one subject practiced Sahaj Marg, which involves focusing on the perception of body sensations and a feeling of lightness and peacefulness in the heart. Therefore, although subjects in the meditation group practiced a variety of different methods, the majority involved a significant component of focus on the body and/or breathing and all involved sustained focused attention as a primary component.

2.3. Measuring emotional responses to pain

To induce painful sensations, we used laser stimuli that specifically activate nociceptors in the skin (Aδ- and C-fibre transmission) due to the absence of skin contact [31]. Using a CO_2 laser stimulator, heat stimuli of 150 ms duration and a beam diameter of 15 mm were applied to the dorsal surface of the subjects' right forearm. Subjects wore protective laser safety goggles during the experiment. Laser stimuli were randomly delivered to different positions on the arm over a skin area of 3 cm × 5 cm in order to avoid habituation, sensitization or skin damage.

An initial psychophysics procedure was performed using a 0–10 numerical scale of pain intensity, which was anchored such that a level 4 indicated just painful (pain threshold). A ramping procedure was repeated three times (up to 30 trials each time) in order to determine a moderately painful level of laser stimulus intensity (level 7 on the scale) for each subject. Participants were told to

Table 1
The main type of meditation practiced by participants in the meditation group, represented in order of their total lifetime meditation experience.

Subject	Main type of meditation	Meditation experience (weeks)
1	Zen	1820
2	Mindfulness of breathing	1612
3	Tantra-Yoga	1040
4	Samatha	884
5	Mindfulness of breathing	832
6	Zen	676
7	Mindfulness of breathing	416
8	Samatha	156
9	Sahaj Marg	156
10	Mindfulness of breathing	78
11	Mindfulness of breathing	52
12	Tantra-Yoga	39

regard 'moderately' painful as halfway between pain threshold and the maximum they could tolerate (which also corresponds to how the level 7 is defined on the scale – halfway between level 4 (threshold) and 10 (tolerance)). A ramping procedure was repeated three times to determine laser intensities rated as a level 7, for each subject. The total length of time of this procedure was 15 min.

The main experiment consisted of two runs of 15 trials, in total lasting 5 min. On each trial of the experiment (Fig. 1a), a laser heat stimulus at a subjective intensity level of 7 was delivered to the subject every 10 s. Subjects therefore received painful stimuli of the same subjective intensity across subjects for the duration of the experiment. Laser stimuli were preceded by the appearance of visual anticipation cues, displayed on a computer monitor in front of the subject, in order to provide subjects with accurate information about the timing of each laser stimulus. The anticipatory cue at –3 s was a black dot; this changed to a grey dot at –2 s and a white dot at –1 s. The white dot was displayed until 3 s after each laser stimulus, when a different visual cue was displayed in order to prompt the subjects to provide a response. The aim was to measure the subjective perception of pain unpleasantness of each individual stimulus. In response to each laser pulse, subjects provided a rating of the unpleasantness using a 0–10 numerical scale, in which 0 was equivalent to "not at all unpleasant", and 10 was equivalent to "extremely unpleasant". Subjects were instructed to focus on the unpleasantness of the pain at all times (during pain anticipation and experience), and were not provided with any other instructions, such as instructions to meditate. In cases where subjects did not appear to follow task instructions adequately at the beginning of the experiment, task instructions were repeated to the subject until the experimenter was satisfied with the level of compliance. Data that was recorded at the beginning of the experiment during periods of non-compliance were not used for analysis.

2.4. Electroencephalographic recordings of anticipatory and pain responses

We measured the brain's evoked response to anticipating and experiencing pain. EEG recordings were taken from 61 scalp electrodes placed according to an extended 10–20 system (EasyCap in combination with a Neuroscan headbox and amplifier system). Bandpass filters were set at DC – 100 Hz, with a sampling rate of

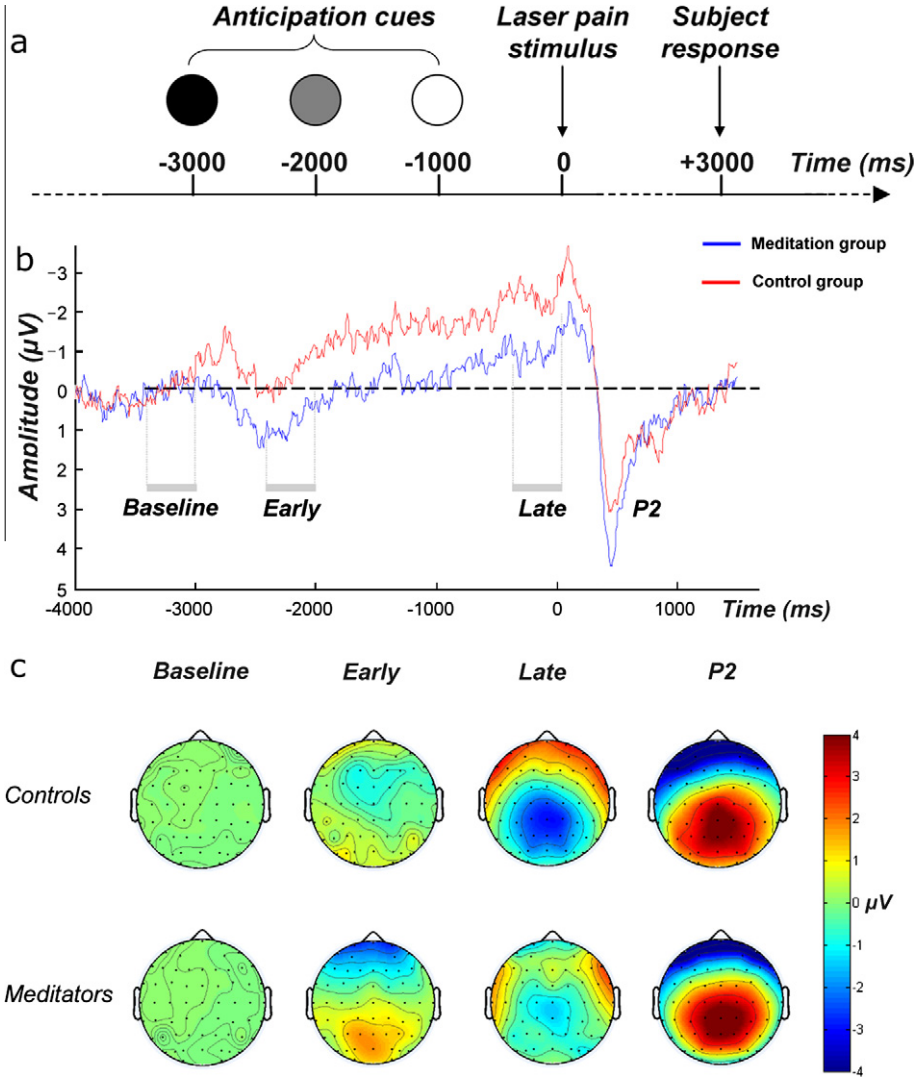

Fig. 1. (a) Experimental design: anticipation and experience of pain. A moderately painful laser stimulus was delivered every 10 s. Prior to stimulus delivery, three consecutive anticipatory visual cues counted down laser stimulus onset. Subjects were cued 3 s after each laser pulse to provide an unpleasantness rating. (b) Grand mean for each group of the anticipatory- and pain-evoked response at electrode CPz. (c) Topographic distribution of anticipatory and pain responses during baseline, early anticipation, late anticipation and P2 peak.

500 Hz and gain of 500. A notch filter was set to 50 Hz to reduce electrical interference. Electrodes were referenced to the ipsilateral (right) earlobe, and recordings were also taken from the contralateral (left) earlobe for off-line conversion to linked-ears reference. The vertical and horizontal electro-oculograms (EOG) were measured for off-line reduction of blink and eye-movement artifacts.

2.5. Analysis of psychological variables

We firstly analyzed post-task pain unpleasantness ratings of laser stimuli by using a Shapiro–Wilk test for normality. Differences between the two groups (meditation and control) were tested using Mann–Whitney *U*-tests. We then sought to determine whether meditation experience (i.e. the total number of weeks spent practicing meditation over the subjects' whole lifetime) predicted variance in pain unpleasantness within the meditation group. To do this, meditation experience was entered into a regression model as the independent variable, with unpleasantness ratings as the dependent variable.

Further analyses were performed to validate relationships between meditation experience and pain unpleasantness ratings, by discounting competing explanations for the variance in the data. One concern was that subjects with longer meditation experience may tend to be older, and that age may also be correlated with the perception of pain. To test this, meditation experience was regressed on the age of subjects. Secondly, we repeated the regression of pain unpleasantness on meditation experience after adding the age of subjects as a covariate, to see if meditation experience explained any variance in pain unpleasantness after controlling for age. Thirdly, in the control group, pain unpleasantness was regressed on age, to determine to what extent the age of subjects without any meditation experience contributed to pain unpleasantness. Lastly, we formally tested for significant differences between the meditation and control groups in the regression of pain unpleasantness ratings on age, by firstly converting the regression coefficients to *z* scores using a Fisher *r*-to-*z* transformation, and secondly determining the probability of not obtaining the difference in the resulting *z* scores.

2.6. EEG data analysis

EEG data were analyzed using Neuroscan Edit 4.3 (Compumedics USA Ltd.). An ocular artifact reduction algorithm [40] was performed. The data were epoched into single trials of 5.5 s duration, starting 1000 ms before the first visual anticipation stimulus and ending 1500 ms after the laser stimulus. Epochs were visually inspected for further ocular artifacts that had escaped automatic removal, and deleted if necessary. Linear trends over the whole epoch were removed using the entire epoch to calculate the linear component in all channels; the whole epoch was used in order to minimize removal of linear trends that may have specifically resulted from the anticipatory neural responses we were intending to measure.

Each epoch was then baseline-corrected to the 500 ms interval preceding the visual anticipation cue. In our initial analysis, this same baseline was used for measuring the anticipatory and the pain-evoked response. An alternative for measuring pain-evoked responses is to baseline-correct during the late anticipation phase (i.e. just prior to pain). This has the advantage that the resulting pain-evoked response would not include any activity that originated during anticipation. This is a more conservative approach, in that Type I errors (resulting from mistaking anticipatory activity for pain-evoked activity) are minimized by removing as much anticipatory activity as possible. On the other hand, it's possible that sources of the anticipatory response may not "carry over" to the pain response, but rather be independently activated during the pain response. Baseline-correcting proximal to the pain stimulus then has the disadvantage of removing these sources from the pain response. This is not simply changing the baseline, but rather removing activity that is common to anticipation and stimulus processing (a Type II error). Considering that both proximal and distal baseline approaches have advantages, we therefore used both when analysing group effects on the pain-evoked response. However, it must be appreciated that Type II errors are preferable over Type I errors, and we therefore favor the more conservative analysis based on the pre-stimulus baseline.

After baseline-correction, trials were averaged separately for each condition. Data were referenced to the common average before proceeding further with data analysis, although ERP waveforms are presented according to the linked-ears reference as is standard practice. Two 500 ms temporal periods of the anticipatory brain response were extracted for analysis. An 'early' period, at −2500 ms to −2000 ms preceding the laser stimulus, was chosen as the earliest part of the anticipatory response that could be measured without interference from visual-evoked responses resulting from the first anticipation cue. A 'late' period, at −500 ms to 0 ms preceding the laser stimulus represented processes taking place in immediate preparation for the impending laser stimulus. These two anticipatory time windows were analyzed on the basis of previous data showing that early and late anticipatory stages respond differently to experimental conditions that modulate top-down processing of pain [7–9]. We therefore expected the different anticipatory stages to respond uniquely to the effects of meditation experience. The P2 peak of the Laser-Evoked Potential (LEP) was also analyzed. For each subject and condition, P2 peak latencies were determined at the electrode for which the P2 peak showed maximum amplitude (CPz). An averaged 20 ms window of LEP data was then extracted, centered on this latency.

For each temporal period (early anticipation, late anticipation, P2 peak) we made a statistical comparison of the amplitude of the ERP between meditation and control groups. We used a non-parametric permutation test (two-tailed) to correct for the multiple comparisons made (detailed in [33]), due to the likelihood of the three tests not meeting the criterion of independence. A two-tailed test was used because although we hypothesized differences in the anticipatory response, we did not specify the direction of the difference, given that both attention and emotional factors are likely to contribute to the amplitude of the ERP with the potential for opposite differences in meditators vs. controls.

2.7. LORETA source analyses

For this analysis we determined sources of the ERP data. Sources were estimated separately for each time period (pre-anticipation baseline, early anticipation, late anticipation and P2 peak) with low-resolution electromagnetic tomography (LORETA), using the LORETA-KEY software [35]. The software uses a three-shell spherical head model registered to the Talairach anatomical brain atlas [42], although the electrode coordinates used were determined from a co-registration between spherical and realistic head geometry that creates a best-fit model [44]. LORETA estimates ERP sources in grey matter volume to a 7 mm^3 grid resolution (2394 voxels in total) using the digitized MNI probability atlas [28]. Time-domain EEG files were converted to current density vector field magnitude using this technique. The resulting LORETA solutions were log transformed at each pixel; this approximates LORETA solutions to a Gaussian distribution for parametric statistical analysis as previously demonstrated [25,26]. LORETA solutions were converted to SPM image format using a modified version of LOR2SPM (http://www.ihb.spb.ru/~pet_lab/L2S/L2SMain.htm). During this process LORETA solutions were intensity normalized in order to eliminate

subject-to-subject global variations. Statistical maps were then created using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5) running on Matlab 7.1 (Mathworks Inc.).

In our initial source analysis we determined regions of the brain activated in common for both the meditation and control groups during early anticipation, late anticipation and the P2 peak separately. Each time period was first contrasted with sources during the pre-anticipation baseline in the control group, and the result was tested in a conjunction analysis against the same contrast in the meditation group. The analysis was repeated on the P2 peak data after baseline-correcting to the pre-stimulus (late anticipation) period, and contrasting to that baseline.

In our second source analysis we set out to uncover group differences in the cortical sources of the anticipatory and pain-evoked ERP. Areas of the cortex were identified that differed between the meditation and control groups during early anticipation, late anticipation and the P2 peak by performing voxel-wise independent-samples *t*-tests. P2 data was analyzed twice, after baseline-correcting both pre-anticipation and pre-stimulus. We also aimed to determine whether there were group differences in the component of the pain-evoked response that was related to anticipatory activity, which may have occurred if any anticipatory activity had "carried over" from the anticipatory time period to the time during stimulus processing (i.e. during P2). This could reveal brain regions which may mediate anticipatory effects on pain. This involved constructing a repeated measures ANOVA on the P2 peak source data in which interactions were determined between the baseline used (pre-anticipation baseline vs. the pre-stimulus baseline, thereby revealing the effect of anticipation during pain processing) and the group (meditation vs. control).

We performed a further analysis that aimed to determine sources of the anticipatory ERP response that predicted pain unpleasantness. We focused on brain activity during the late anticipatory and P2 peak periods (analyzed once for each baseline used), when the group differences were evident in the source data. The meditation and control group's source data were contrasted after entering pain unpleasantness ratings as a covariate of interest.

For all of the above statistical tests on source data, sources were initially identified that fell below the threshold of significance of $p < 0.001$ (two-tailed, uncorrected for multiple comparisons), with a minimum of three contiguous voxels, for volumes of interest (VOIs) known to vary with pain anticipation and experience, and which previous studies have shown to be modified as a result of meditation (these areas were the insular, somatosensory, cingulate, prefrontal and parietal cortices). For results in all other brain areas, results were only accepted if surviving whole-brain correction for multiple comparisons using False Discovery Rate (FDR) at $p < 0.05$ with a minimum of three contiguous voxels.

2.8. Analyses of volumes of interest

We extracted data from VOIs identified in the previous analyses in order to plot times-courses and to regress against variables of interest. During pain anticipation, these VOIs were midcingulate cortex (MCC), right inferior parietal cortex (IPC), and medial prefrontal cortex (mPFC) (the mPFC cluster included pregenual anterior cingulate cortex (pACC)). During pain experience, the two VOIs identified were contralateral (left) insula and ipsilateral (right) S2 cortex. VOIs were extracted as the first eigenvector (i.e. the mean of the adjusted response after rejecting noise) across voxels that were above the chosen statistical threshold within a cluster. These values were then corrected to the group mean.

Time-course plots were created by extracting the data from each VOI for each time period separately (baseline, early anticipation, late anticipation and pain (P2 peak, with pre-anticipation baseline)). These data were then plotted as the mean activity for each group at each time period after correcting to the baseline activity in that volume (i.e. the activity prior to the anticipation cue).

We then sought to determine whether the level of meditation experience explained variance in the VOIs identified. In order to do this, we created a number of regression models with each VOI (5 in total) from the above source analyses as a dependent variable and meditation experience as an explanatory independent variable. VOIs were considered significantly predicted by meditation experience after applying a two-tailed statistical test using Pearson's coefficient.

Pain unpleasantness was then regressed on to the significant VOIs to determine if these VOIs predicted the psychological data. Significant regressions in the meditation group were tested against the same regressions in the control group to determine if they were significantly different using a univariate ANCOVA model in which pain unpleasantness scores were entered as the dependent variable, group was entered as a fixed factor, and VOI activity was considered as a random factor.

Lastly, we tested whether brain activity predicted by meditation experience was also predicted by age in the control group, to discount the possibility that we were simply observing age effects on brain activity. To do this, age was entered into a regression analysis as an independent variable, with each VOI as a dependent variable.

3. Results

3.1. Laser intensities

We performed an initial analysis of group differences in the laser energies required to reach pain threshold and to induce a moderate (subjective level 7) sensation of pain. For the meditation group, pain threshold was reached at a mean (SD) laser energy of 2.02 (0.44) Joules, and moderate pain at 3.62 (1.12) Joules. For the control group, pain threshold was achieved at 1.8 (0.32) Joules and moderate pain at 3.02 (0.84) Joules. Despite a higher mean energy being delivered to the meditation group, these differences were not significant ($p = 0.20$ for pain threshold, and $p = 0.12$ for moderate pain).

3.2. Psychological data

No significant differences were found in perceived pain unpleasantness between the meditation and control groups when considering the whole sample (see Fig. 2a). We repeated the analysis including only participants in the meditation group with six or more years of meditation experience (resulting in $n = 7$ in the meditation group), who were also the youngest in the group. To create an age-matched control group for comparison, we removed the five youngest from the control group (the differences in ages between the resulting two groups was then non-significant at $p > 0.15$). The resulting group effect on pain unpleasantness was then found to be significant ($p < 0.03$, Fig. 2b).

Within the meditation group (whole sample of $n = 12$), meditation experience negatively predicted ratings of pain unpleasantness ($r = -0.68$, $p < 0.01$; Fig. 2c). However, the age of the subjects strongly predicted meditation experience in the meditation group ($r = 0.81$, $p < 0.001$; Fig. 2d), as well as predicting pain unpleasantness ratings in this group ($r = -0.86$, $p < 0.001$). When age was entered as a covariate into the regression model comparing meditation experience with pain unpleasantness, meditation experience was not found to account for any further variance in pain unpleasantness ratings beyond that accounted for by age ($\beta = 0.05$, $p > 0.86$). However, due to multicollinearity of the independent variables (age and meditation experience) within the regression model,

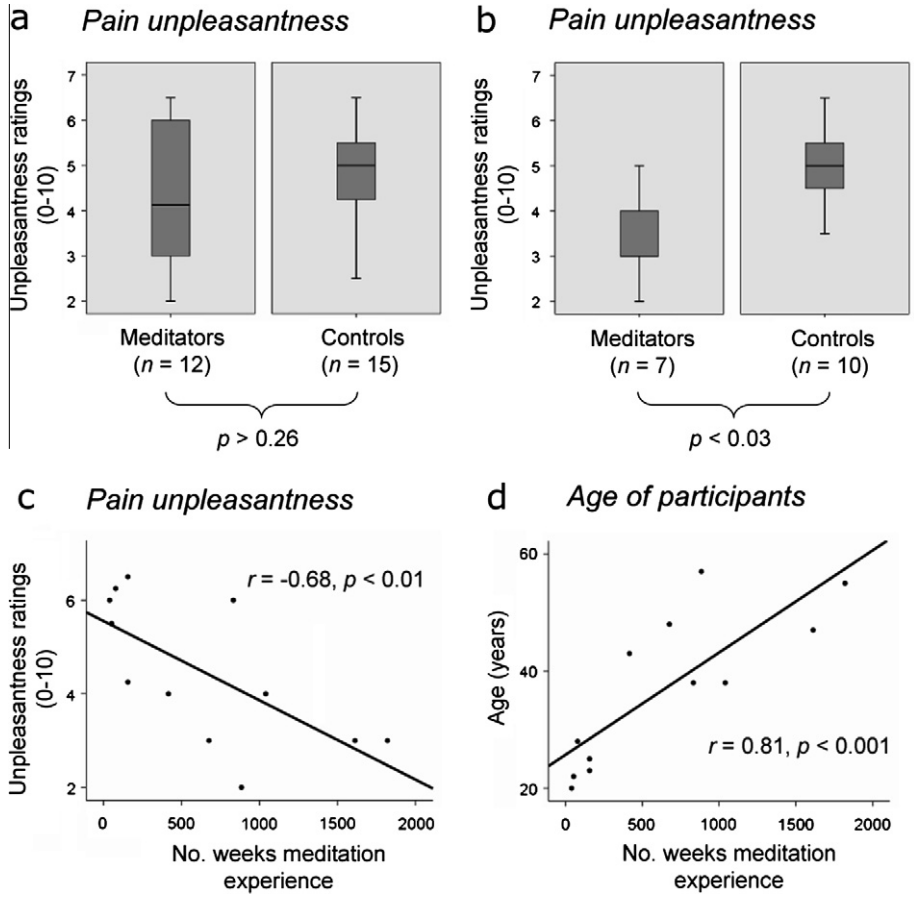

Fig. 2. (a) Box-and-whisker plot showing non-significant group effects (meditation vs. control) on pain unpleasantness ratings. The boxes indicate the inter-quartile range, whilst the whiskers indicate the full range. (b) The same data is represented as in plot (a) but with the number of subjects in each group reduced, such that only experienced meditators with six or more years of practice are contrasted to an age-matched control group. Also shown are scatter plots showing significant correlations of meditation experience with (c) pain unpleasantness ratings and (d) the age of subjects.

we can not draw conclusions from these results. Hence we relied on data from the control group to determine whether variance in pain unpleasantness could be accounted for by age. In this model, age was not found to be predictive of pain unpleasantness ($r = -0.17$, $p = 0.55$). Using a Fisher r-to-z transformation, we calculated the probability of there being no difference between meditation and control groups in the regression of age with pain unpleasantness ratings to be less than 0.01.

3.3. EEG results

As confirmation of the group difference in anticipatory ERP amplitude visible in Fig. 1c, the results of the non-parametric test revealed a significant difference between the meditation and control groups during the late anticipatory stage ($t = 2.51$, $p < 0.05$), but not during the P2 peak of the pain-evoked potential ($t = 0.65$).

The expected sources of the anticipatory and pain-evoked response in the pain matrix were revealed in the conjunction analysis to be in common to both the meditation and control groups (Fig. 3a–d). Furthermore, across the early anticipation, late anticipation and P2 peak periods, a subset of areas were activated in common to both groups across all three time periods. These brain regions included: bilateral posterior insulae, right (ipsilateral) parietal operculum, midcingulate cortex (MCC), posterior cingulate cortex (PCC, restricted to the left hemisphere during early anticipation, but in the right hemisphere during late anticipation and pain), inferior parietal (IPC), precentral and postcentral cortices. A number of further regions were activated that are not directly relevant to the current analysis (see Supplementary data). Only minor differences were observed in the common sources of the P2 peak when comparing data baselined pre-anticipation (Fig. 3c) and pre-stimulus (Fig. 3d; see also Supplementary Table 3), with sources in the hippocampus and middle temporal gyrus appearing more prominently in data corrected pre-stimulus.

Areas of the cortex were identified that differed between the meditation and control groups during late anticipation and pain. The meditation group showed lower activation of MCC and right IPC during late anticipation relative to the control group (Table 2, Fig. 4a). By masking the results with sources of activation in the control group only, we found that the MCC source was activated during late anticipation in the control group, whereas activation of right IPC was not found (due to this region not meeting the threshold of the mask applied, at $p < 0.001$). During pain, when data was baseline-corrected to the pre-anticipation period (Fig. 4b), lower activations were found in the meditation group in right somatosensory cortex (S2, ipsilateral to the stimulus) and left posterior insula (contralateral to stimulus), despite no difference in P2 peak amplitude. Both of these areas were activated in the control group during pain experience. However, due to limitations in our experimental design, pain-evoked activity may have contained significant anticipatory activity. A more conservative approach is therefore to use a pre-stimulus (late anticipation) baseline, which would remove any pain-evoked activity carried over from the anticipation response. When the pain-evoked response was baseline-corrected to the pre-stimulus period, no significant group effects were found.

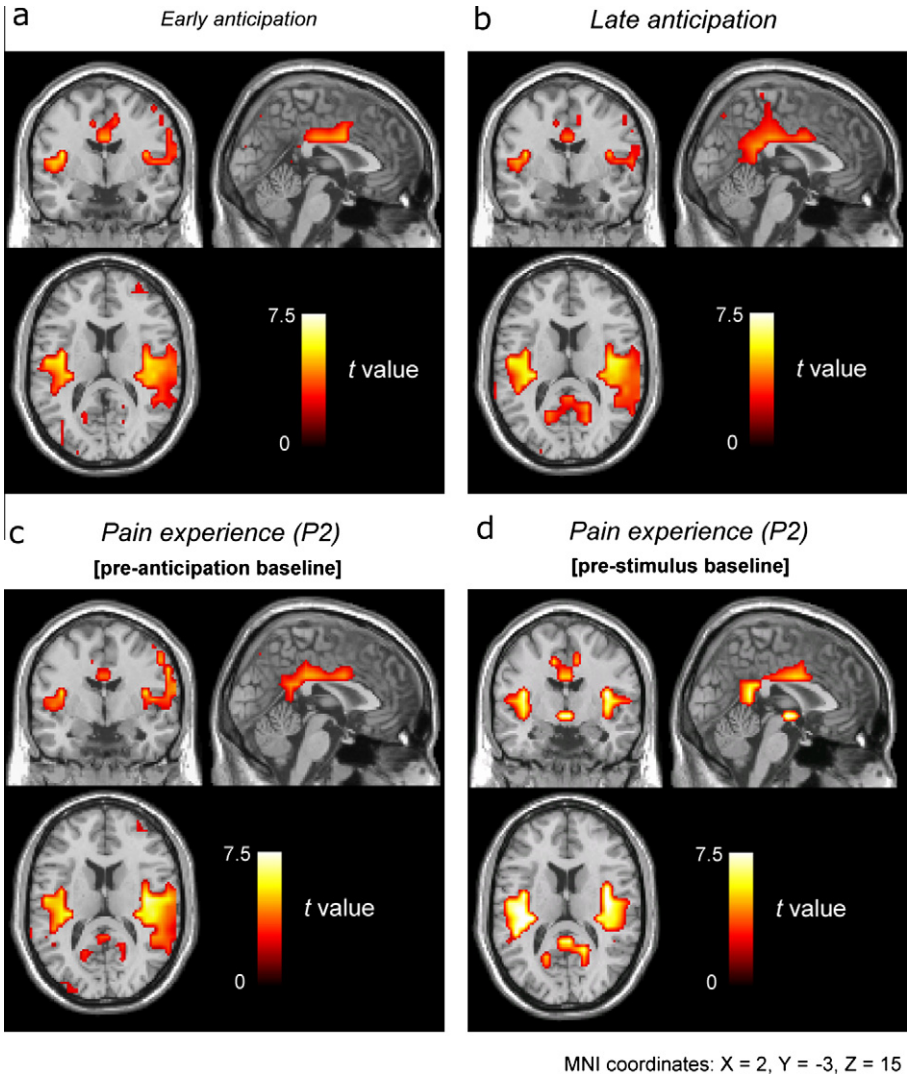

Fig. 3. (a) LORETA source results showing common areas of anticipatory and pain processing between the meditation and control groups (conjunction analysis). The P2 peak (pain-evoked response) data is presented twice: once after baseline-correcting to the pre-anticipation period, and once after correcting to the pre-stimulus (late anticipation) period. See Supplementary material for a full list of regions activated.

Significant interactions were found within the P2 source data between the group variable (meditation vs. control) and the different baseline periods used (pre-anticipation vs. pre-stimulus). This analysis reveals group differences in the effects of anticipation during the pain-evoked response. The results (Fig. 4c) show that anticipatory MCC activity was lower in the meditation group

Table 2
Brain regions showing groups differences in current density during anticipation and pain.

Brain region		Area	MNI coordinates			*z*-Score	*p*-Value (uncorr)
			x	*y*	*z*		
Controls > meditators							
Late anticipation							
Midcingulate cortex	L	24	−3	−4	29	3.32	0.000
Inferior parietal cortex	R	40	53	−60	43	3.01	0.001
Pain							
Secondary somatosensory cortex	R	40	60	−25	22	3.93	0.000
Insula cortex	L	13	−45	−4	8	3.06	0.001
Interaction between group and pain unpleasantness							
Late anticipation							
Medial prefrontal cortex	R	10	11	52	15	4.10	0.000
Interaction between baseline (pre-anticipation vs. pre-stimulus) and group							
Pain							
Midcingulate cortex	R	24	4	−4	29	3.43	0.000
Medial prefrontal cortex	R	10	4	66	8	3.49	0.000

Uncorr, uncorrected *p*-values; Area, Brodmann's area.

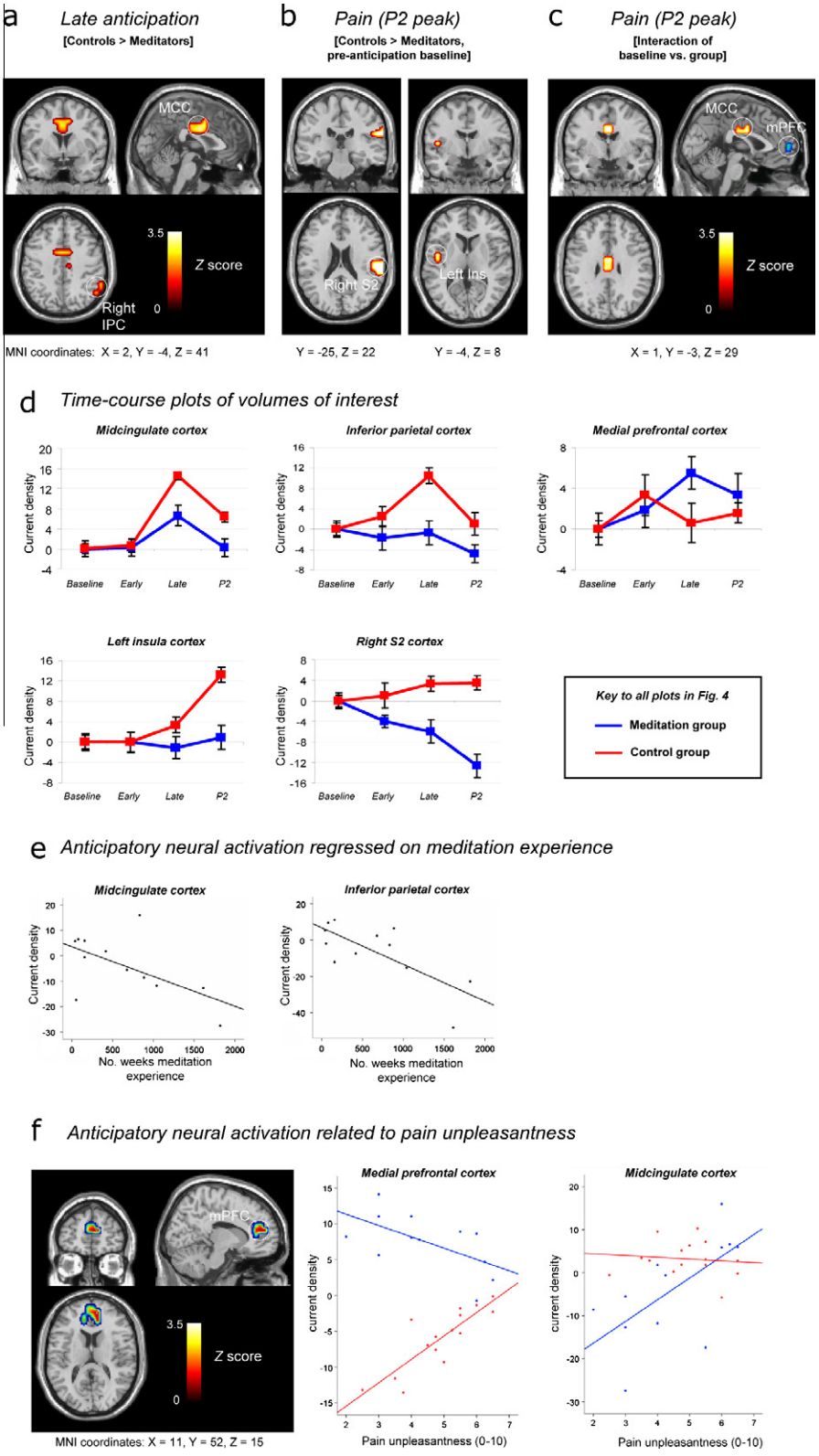

Fig. 4. (a) LORETA source results of the contrast between meditation and control group during late anticipation. (b) The contrast between meditation and control group during pain. (c) Results of the interaction between baseline used for analyzing the P2 peak (pre-anticipation vs. pre-stimulus) and group (meditation > control group is represented in blue, control > meditation group in red) on P2 peak source data. (d) Time-course plots of each volume of interest that showed significant group effects, with each group represented separately, and with data baseline-corrected to the pre-anticipation period. "Baseline" refers to the pre-anticipation baseline, "early" refers to early anticipation, "late" refers to late anticipation, and "P2" refers to the pain-evoked response. Error bars indicate the standard error of the mean. (e) Brain regions revealed in the (control > meditation) group contrast on the late anticipation period, showing inverse correlations with meditation experience. (f) Brain regions showing correlations with unpleasantness ratings during late anticipation. The mPFC/pACC region was revealed in the interaction between pain unpleasantness ratings and group (control > meditation). Midcingulate cortex has a positive correlation with pain unpleasantness in the meditation group but not the control group. All data from VOIs in this figure were mean-corrected prior to analysis. MCC, midcingulate cortex; IPC, inferior parietal cortex; Ins, insular cortex; S2, secondary somatosensory cortex; pACC, pregenual anterior cingulate cortex; mPFC, medial prefrontal cortex.

relative to the control group during pain processing, whereas mPFC activity was higher in the meditation group.

Plots of the time-course of activity in each volume of interest are shown in Fig. 4d, with the two groups represented separately to allow for comparison of at which time period(s) neuronal activity diverges. Group differences in MCC and left posterior insula were not apparent until late anticipation. At that time, the MCC peaked in both groups but was larger in the control group. Insula activity did not increase at all in the meditation group, but gradually increased over time in the control group, peaking during the pain-evoked response. Two more lateral areas of the pain matrix, right IPC and S2 cortex, started to show group differences during early anticipation, although the differences did not reach statistical significance until late anticipation and pain respectively. Activity in S2 cortex actually decreased over time in the meditation group, opposite to the response in the control group. The preliminary divergence of activity in left insula and right S2 between groups during anticipation may explain why these effects were not significant after baseline-correcting the pain-evoked data to the pre-stimulus period, which would have removed the already substantial group differences at this time and biased the data during pain. Activity in mPFC showed an early increase in both groups but diverged during late anticipation to be greater in the meditation group, although the effect was not statistically significant.

Differences were identified between the meditation and control groups in the regression of pain unpleasantness ratings on cortical activation during late anticipation (Table 2 and Fig. 4f). The region identified was in medial prefrontal cortex (mPFC), including pregenual anterior cingulate cortex (pACC). Whereas in the control group, mPFC/pACC showed a strong positive relationship to pain unpleasantness, meditators showed a negative relationship of pain unpleasantness with activity here, scatter plots of which are shown in Fig. 4f. Notably, activation in mPFC/pACC was higher overall in the meditation group than the control group – this result did not survive our threshold during the initial LORETA whole-brain comparison between groups, but did reach significance after removing the 5 least experienced meditators and comparing them to an age-matched control group (by removing the 5 youngest members of the control group). Similar levels of activity are evident in both groups as pain unpleasantness ratings reach the high end of the scale, as shown by the convergence of the two best-fit regression lines. The analysis of group differences in the regression of unpleasantness ratings on P2 peak source data did not reveal any significant effects.

3.4. Regression analyses in volumes of interest

Within the meditation group, VOIs during anticipation and pain were regressed on to meditation experience (Fig. 4e). Meditation experience predicted lower activation of inferior parietal ($r = -0.64$, $p < 0.03$), and midcingulate cortices ($r = -0.59$, $p < 0.04$) during late anticipation of pain. Neither of these VOIs were found to be predicted by age in the control group (overall adjusted $r^2 = -0.07$, $p > 0.57$). In regressing the unpleasantness ratings data on VOIs (Fig. 4f), lower anticipatory MCC activity predicted lower pain unpleasantness in the meditation group ($r = 0.64$, $p < 0.03$), but not in the control group ($r = -0.12$, $p > 0.70$). The relationship between anticipatory MCC activity and pain unpleasantness was significantly greater in the meditation group than in the control group ($p < 0.03$). An ANCOVA model also revealed a statistically significant interaction between the group and pain unpleasantness ratings in explaining variance in MCC activity ($p < 0.05$). In addition, we found that the inverse relationship between anticipatory activity in mPFC/pACC and pain unpleasantness in meditators (contrary to the positive relationship in controls) could be partially explained by MCC as a mediating variable ($p < 0.03$), using a Sobel test for mediation. However, when activity in the same region of MCC was analysed during pain, it did not predict unpleasantness ratings when baseline-corrected pre-anticipation ($r = -0.39$, $p > 0.21$) or pre-stimulus ($r = 0.13$, $p > 0.69$).

4. Discussion

When groups of meditators and matched controls have been compared in previous studies, inconsistent group effects have been shown on subjective pain experience [18,32,34]. In the present study, significant group effects were not found until the youngest members of each group were removed from the analysis – this included any meditators with less than six years of experience. Furthermore, greater meditation experience correlated with a lower perception of pain unpleasantness. Although this variance was almost entirely accounted for by the age of the subjects in the meditation group, age did not explain any variance in pain unpleasantness in the control group. Meditation experience, therefore, appears to account for variance in pain unpleasantness that cannot be explained by the age of the participants.

The effect of meditation experience on pain unpleasantness ratings could derive from a lower emotional response to the actual pain stimulus, lower negative emotional appraisal of the forthcoming pain during anticipation, or a reporting bias related to other cognitive factors. The aim of our study was to determine whether anticipatory or pain-evoked responses could explain possible effects of meditation on the emotional appraisal of pain. The pain matrix was commonly activated by both meditation and control groups during anticipation and pain. However, group differences were found in the anticipatory neural response: the meditation group produced a lower anticipation-evoked potential relative to controls, revealed by source analysis to result from lower activation of right inferior parietal cortex (IPC) and midcingulate cortex (MCC). Greater lifetime meditation experience predicted the lower activity of these regions.

Group differences were also found in the component of the pain-evoked response related to anticipatory activity, derived by comparing the P2 peak sources when baseline-corrected pre-anticipation vs. pre-stimulus. Meditators had lower activity in MCC, but higher activity in medial prefrontal cortex (mPFC). When P2 sources were analyzed that included anticipatory activity (i.e. baseline-corrected to the pre-anticipation period), group differences were also observed. Meditation was associated with lower activation of right (ipsilateral) S2 and left (contralateral) insula. However, when anticipatory activity was subtracted out of the pain-evoked activity (by baseline-correcting pre-stimulus), there were no longer any group differences in the pain-evoked response. It's therefore possible that group differences in the pain-evoked response were dependent on differences in anticipatory processing, although our experimental design did not allow for pain-evoked activity to be assessed independently of the preceding anticipatory response.

We looked at group differences in the way neural activity evolved over time, from pre-anticipation, through early and late anticipation, to pain. Of interest here was the data showing that group differences in anticipatory activity in MCC, IPC and perhaps mPFC continued into the pain-evoked response, although to a lesser extent compared to during anticipation. Also, group differences in left insula and right S2, largest during pain, began to become evident during anticipation. The above is further evidence that the effects of meditation on pain processing derived from differences in anticipation.

4.1. The effects of anticipatory processing on negative appraisal

Considering that the meditation group primarily differed from the control group in their anticipation of pain, it would be expected that anticipatory activity would also predict the observed differ-

ences in the perceived unpleasantness of the painful laser stimuli. Indeed, we found strong evidence that this was the case. As previously discussed, meditation experience predicted anticipatory neural activity in MCC. This activity in MCC, in turn, predicted unpleasantness ratings in the meditation group. However, anticipatory MCC activity did not predict unpleasantness in the control group. This suggests that the relationship between lower MCC and lower pain unpleasantness was a function of meditation experience. Furthermore, although anticipatory activity in MCC predicted pain unpleasantness, activity here during the pain-evoked response did not. This data is consistent with the hypothesis that meditation primarily reduces the negative appraisal of pain during anticipation. However, it's possible that pain-evoked activity beyond the time of the P2 peak (which was not analyzed) may have also related to pain unpleasantness.

As introduced earlier, meditation can be regarded as training in cognitive control, and has been associated with improved functioning of cognitive control networks [6,20,21,41]. It would be expected that such networks would be required to modify pain anticipation and appraisal. The mPFC, bordering on pregenual anterior cingulate cortex (pACC), is a region known to be involved in signaling the need for cognitive control during the perception of threat [3,4]. Research using fMRI has located increased activations within mPFC/pACC as subjects engage in meditation [20], and activity in this region during affect labeling correlates with self-reported levels of dispositional mindfulness [13].

In our study, anticipatory activity in mPFC/pACC predicted the unpleasantness of pain in control group participants. It is already understood that bottom-up processes of threat perception (e.g. deriving from early processing in visual cortices) can reach the amygdala via a 'fast' pathway to signal a perceived threat [4]. This results in a further signal to mPFC/pACC for greater cognitive control. This is analogous to what happened in our study once participants viewed an anticipation cue. Hence, anticipatory mPFC/pACC activity would be expected to correlate with the level of perceived threat, consistent with its relationship to unpleasantness ratings in the control group. If meditation could induce cognitive control in advance of a threatening cue (rather than in response to it), the level of mPFC/pACC activity would be expected to be inverse to the level of perceived threat. This idea is consistent with our data in the meditation group: anticipatory mPFC/pACC activity predicted lower unpleasantness ratings, an effect mediated by the lower activity in MCC.

4.2. Mechanisms of cognitive control in meditation

There are two specific aspects of meditation training that may reduce anticipation of pain. When meditators learn to control attention, they also cultivate an attitude of acceptance [5,19,29]. Acceptance promotes cognitive control by reducing engagement with emotional appraisals of perceived events, which would otherwise serve as a distraction [30,38,39]. Therefore, acceptance is a precursor for effective cognitive control. Lower MCC and right IPC activity during anticipation may be related to less attention to affective appraisals of future pain. Variance in pain processing in MCC and right IPC has been previously linked to attentional functions; anticipatory MCC activity predicts automatic attentional orientation towards pain [14,37], whereas right IPC has a more executive role related to voluntary spatial orienting [2,12,16,17,36].

Alternative explanations exist for the lower activations in both MCC and IPC in meditators. The results could imply relatively less attentional engagement with the pain or with the task. However, the aim of mindfulness meditation is to attend carefully to pleasant, unpleasant and neutral stimuli equally and with acceptance of those experiences. It therefore seems unlikely that meditators would choose to distract themselves from pain as a coping strategy.

4.3. Limitations of this study

Among the limitations of the study are the small sample size and our reliance on regression analyses to investigate the effects of meditation experience. Because meditation was not part of the experimental manipulation, it is uncertain how causative meditation experience was in determining our results. Ideally, research studies aiming to investigate the mechanisms of meditation would benefit from including the practice of specific meditation techniques as part of the experimental manipulation. As with any kind of expertise research, cross-sectional studies or perhaps longitudinal studies without randomized controls are the best data that will ever be available. Such studies could reduce potential confounds by improving control matching across a range of criteria, for example balancing subjects in the meditation and control groups according to their educational level.

It's also not clear from our data whether the differences found between the meditation and the control groups relate to differences in attention, acceptance, or both. Personality traits that determine who is likely to take up and sustain a meditation practice may also be predictive of our data, rather than expertise in meditation.

Our experimental design did not allow for the assessment of pain-evoked neural activity independently from the preceding anticipatory response. Using a pre-stimulus baseline for analysis of the pain-evoked response may remove activity that also occurs during anticipation, but a pre-anticipation baseline may result in anticipatory activity that is carried over into temporal window of stimulus processing. An improved design could include some uncued trials to identify pain-evoked activity that is more independent of anticipation. Furthermore, pain-evoked activity related to processing pain unpleasantness may have extended beyond the relatively early P2 peak analyzed, but for design efficiency subjects gave unpleasantness ratings too soon after the pain stimulus (3 s) to allow for artifact-free data to be analysed much beyond the P2 peak.

5. Conclusions

Our data is consistent with the hypothesis that meditation reduces the anticipation and negative appraisal of pain. This has implications for the use of mindfulness meditation in chronic pain: individuals whose pain is strongly influenced by anticipation may benefit most. However, further work is required to directly test the causal relationship between meditation, pain anticipation, and pain experience, using experiments that can assess pain processing independently from anticipation.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2010.04.017.

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