Psychobiological Correlates of Improved Mental Health in Patients With Musculoskeletal Pain After a Mindfulness-based Pain Management Program

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Objectives: Mindfulness-based pain management programs (MBPMs) aim to improve mental and physical health in individuals with chronic pain. In this study, we investigated whether improvement in mental health might require (1) reduction in the sensory pain experience and brain correlates of that experience, and/or (2) improved perceptions of the controllability of pain and corresponding brain activity related to cognitive control and emotional regulation.

Methods: Twenty-eight patients with chronic pain were assessed and randomized into an intervention group (who attended an 8-wk MBPM) or a control group (treatment-as-usual), before being reassessed after 8 weeks. Outcome measures included clinical pain, perceived control over pain, mental and physical health, and mindfulness. Neural activity was measured during the anticipation and experience of acute experimental pain, using electroencephalography with source reconstruction.

Results: Improvements were found in the MBPM group relative to the control group in mental health, which related to greater perceived control of pain, but not to reductions in clinical or experimental pain ratings. Anticipatory and pain-evoked event-related potentials to acute experimental pain were decreased, but sources of these event-related potentials were estimated to be in regions that modulate emotional responses rather than pain intensity. Mental health and perceived control outcomes correlated with reduced anticipatory deactivations of dorsolateral prefrontal and somatosensory cortices.

Discussion: Increased activity in cognitive control regions of the brain during pain anticipation related to improved mental health and perceived control over pain, but not to decreased pain experience. Greater perceived control may therefore result from improved regulation of the emotional response to pain.

Key Words: pain, anticipation, meditation, mindfulness, attention, EEG, nociception

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Mindfulness-based interventions teach psychological skills that can improve the quality of life of individuals with long-term conditions,[1,2] including those with chronic pain.[3,4] However, significant effects on physical symptoms such as pain are less commonly reported than mental health and other quality-of-life outcomes.[3–5] There is no evidence that a reduction in physical symptoms is needed before improvements in psychological functioning can be observed. On the contrary, definitions of mindfulness suggest that the aim is not to bring about particular desired states or experiences, but rather to accept experiences as they are without reacting to them or judging them negatively.[6] It is therefore clear that the main aim of mindfulness programs for pain is not sensory pain reduction, but rather better control over the cognitive and emotional aspects of pain, and it is this that defines the usefulness of mindfulness within a pain self-management context.

To establish whether mindfulness-based interventions achieve this goal, evidence is required that improvements in mental health are not dependent on a reduction in the sensation of pain, but rather relate to perceptions of the controllability and manageability of the cognitive and emotional components of pain. This is thought to depend on the ability to attend to experiences in the present moment, and to withdraw attention from ruminative thinking based on past and future.[6] Psychometric scales exist that specifically measure this aspect of mindfulness in a person,[7] which have been related to positive coping in chronic pain populations.[8] However, it has not been clearly demonstrated that the mental health benefits of this training are related to improved perceptions of control over the pain response rather than a reduction in perceptions of pain sensations.

In the current study, we investigated the effects of a mindfulness-based pain management program (MBPM) on mental health, while also measuring changes in the perceived level of control over pain, readiness to engage in a self-management approach to pain, clinical pain symptoms, and the attentional aspects of mindfulness as a potential mediator of these effects. Perceived control was of particular interest as a construct that has previously been related to pain processing and perception,[9,10] mental health outcomes,[11,12] and coping ability.[13]

Research into mechanisms of psychotherapeutic action should ideally include data across biological, cognitive, and behavioral levels.[14] Although psychometric outcome measures can be useful for understanding how interventions work, a complementary approach is the use of brain imaging. Brain imaging provides the ability to probe the biological effectiveness of a psychological intervention, especially in terms of whether sensory pain processing per se is affected, or whether secondary (emotional and/or cognitive) processes are affected. Better definition of the biological processes involved

may, in the future, aid in better targeting treatments based on consideration of the patients' psychological and biological profile. Human brain imaging data may be considered more objective than psychometrics, but at the expense of being more difficult to interpret, requiring reference to correlations with psychometric and behavioral data.

Studies have shown that mindfulness training improves executive brain functioning[15–18] and affects associated neural processes.[19,20] Increased dorsolateral prefrontal cortical (DLPFC) activity, in particular, has been associated with states of mindfulness meditation,[19,21] cognitive and behavioral control,[22] emotional regulation,[23] and perceived control over pain.[24] From this evidence, we hypothesized that mindfulness training would be associated with increases in DLPFC activity during anticipation of pain, when there is an opportunity for emotional regulatory strategies to be executively used. We also hypothesized these changes would be related to mental health and pain control/self-management outcomes, rather than a reduction in pain. Such changes in DLPFC might therefore reflect improvements in cognitive and emotional responses to pain, rather than reductions in pain itself.

To examine neural activity, we used a method published previously[25] in which we induced experimental laser pain, rather than clinical pain. Owing to the brevity of the laser stimuli, this enabled separate measurements of neural activity relating to pain anticipation and pain experience using electroencephalography (EEG), which would be challenging to achieve by stimulating clinical pain. Our previous work[25] showed that long-term meditation experience (over years/decades) was associated with less perceived unpleasantness of experimental pain, with concurrent reductions in pain processing in the midcingulate cortex. However, the study was a case-control design and relied on correlations between reported meditation experience and outcomes in a nonpatient group, which has clear limitations as discussed elsewhere.[26] Although the experimental methods used in the current study were almost identical to the previous study, this study expands on that work by measuring clinical outcomes and neural activity in a clinical pain population, and comparing identical measurements before and after a mindfulness intervention.

MATERIALS AND METHODS

Ethics Statement

The research study was approved by North Manchester Local Research Ethics Committee in the United Kingdom. Written informed consent was obtained from study participants.

Study Design

The study was a 2×2 factorial design with one factor being group (an intervention group and a control group), and the other factor being time (first and second experimental sessions). There was a 2-week window, either side of the treatment, during which we scheduled patients for experimental visits. Because this depended on patient availability, there was some variation between participants in how far apart the 2 experimental sessions were, and this varied between 8 and 12 weeks. Patients in the control group were scheduled for their visits according to a comparable timeframe.

Between experimental sessions, the intervention group participated in an MBPM, run by Breathworks Community Interest Company, entitled Living Well with Pain and Illness. The details of this intervention and some of the impact on patients with chronic pain have been documented elsewhere.[27] The program consisted of a total of 20 hours of training (2.5 h/wk for 8 wk). The program teaches not to try to do anything about the underlying unpleasant sensation of pain, but to train in mindfulness to lessen the reactive cycle that leads to physical and emotional stress. This is done by teaching breath awareness, body awareness, gentle movement, training in how to manage pain, illness and fatigue in daily life, and cultivating kindliness and compassion toward oneself and others. The main components of the program are:

1. *Breath awareness*: Investigating breathing habits, learning to use the natural breath as an aid to managing pain, illness, or stress, developing habits of breathing into difficult experiences to soften resistance to pain or illness and to let go of tension.
2. *The body scan*: Developing greater awareness of the body by "scanning" through the whole body with careful attention, using the breath to help let go of areas of pain and/or tension.
3. *Mindful movement*: Stopping the cycle of disuse, loss of function and more pain or fatigue with some gentle movements, based on yoga and pilates.
4. *Mindfulness of daily life* (*pacing*): Bringing awareness to the activities of daily life to prevent overdoing on good days and collapsing on bad days. This involves using diaries and symptom scoring to become more aware of what activities cause aggravation, and then to make conscious choices toward a more balanced approach to life.
5. *Three-minute breathing space*: Taking 3-minute breaks in the midst of activity to rest awareness with the breath.
6. *Mindfulness of breathing*: Focusing on the breath in order to learn to reduce the activity of the mind, making it easier to watch our thoughts, feelings, and sensations come and go without judging them, identifying with them or pushing them away.
7. *Kindly awareness*: Firstly spending time becoming aware of the unpleasant and the pleasant aspects of experience in the present moment. Then, broadening to include other people and developing empathy by reflecting on what is shared by all: the breath, pleasure, pain, and eventually, the sickness and degeneration that comes with age. Between the first and second sessions, control group participants continued with treatment-as-usual, and were given the option of participating in the mindfulness course after completing the second session.

Participants

The recruitment of participants for the study was advertised as open to right-handed patients with any type of musculoskeletal pain. Patients were excluded from the study if their medical records showed a history of neurological, psychiatric, or cardiovascular disease. Our aim was to recruit patients with "normal" levels of distress for a chronic pain population, which would be elevated compared with a healthy population, but to screen out major psychiatric disorder that had been diagnosed by a specialist. These included patients with major depression, bipolar disorder, anxiety disorders (obsessive compulsive disorder, panic, phobias, generalized anxiety disorder), and schizophrenia. It was expected that many patients recruited would be likely to have mild to moderate levels of anxiety and/or depression that had not be diagnosed.

To power the study, our primary concern was to test for neurobiological effects of the intervention, particularly differences in anticipatory responses. We based the power calculation on data obtained from a case-control study published previously[25] in which healthy volunteers with an established meditation practice showed significant differences in the amplitude of the anticipatory-evoked potential compared with those without meditation experience. The mean amplitude of the response in the meditation group was −1.09 and in the control group was −2.50, with SDs of 1.17 and 1.94, respectively. This amounts to an effect size of 0.89. At 80% power and an α-level of 0.05 in a 1-sided test, this would require 17 participants per group to show a statistically significant effect. We therefore aimed to recruit 20 patients to each group in the present study to see whether similar differences could be found comparing preintervention and postintervention data. In the end, our dropout rate caused this target to be missed (for details on dropouts, see below).

Patients were screened as follows. A total of 1014 patients were screened using electronic medical notes. Five patients were excluded on the basis of prior history of psychiatric disorders. A total of 1009 patients were invited to take part in the study. Of these, it was found that 91 did not meet the inclusion criteria for reasons not detailed in their medical notes (eg, many were left handed). A total of 343 patients declined to take part, whereas there was no response from 535 patients. A total of 40 patients were recruited.

All 40 participants gave informed written consent. Patients were randomized into 1 of 2 groups: an MBPM group and a control group. Patients were allocated to 1 of 5 MBPM courses, according to their availability, that were also open to self-referring participants not involved in the study, with a maximum of 15 participants per course. Of the original 40 patients, a total of 9 dropped out of the study, 5 from the control group and 4 from the intervention group. Of the 4 who dropped out from the intervention group, one did so after the initial experimental session but before the pain management course, one did so after the first week of the course, one after the second week of the course, and the fourth after completing the course but before the second experimental session. Unfortunately, we were not able to establish the reason why all patients dropped out when they did. We have documented reasons for 6 of the 9 dropouts. The remaining patients did not provide details of their reasons for discontinuing. Of the patients who gave reasons, 2 dropped out because they found the experimental pain procedure too unpleasant to want to return a second time, 1 experienced family bereavement, 1 needed a medical operation, 1 started a new job and it was not practical to attend the treatment sessions, and 1 was diagnosed with significant psychiatric comorbidities and recommended not to continue with the study by a psychotherapist. Of the remaining 31 patients, 3 were found to have poor-quality EEG recordings, reducing the number to 28. In the end, 15 patient data sets were completed in the MBPM group, and 13 in the control group.

The details of the 28 patients whose data were analyzed are as follows. The clinical diagnoses of all patients are shown in Table 1, from which is it clear that most patients (18/28) had been diagnosed with fibromyalgia. The intervention group contained 8 patients with fibromyalgia (2 with arthritic comorbidities) and the control group contained 10 patients with fibromyalgia. The mean age of patients in the intervention group was 48 ± 10, and in the control group was 45 ± 12. Independent samples t test statistics revealed no significant difference between the ages of the 2 groups. The intervention group was composed of 12 females and 3 males, whereas the control group contained 9 females and 4 males.

TABLE 1. Numbers Recruited Into the Study According to Diagnosis and Group

	No. in Each Group	
Diagnosis	**Intervention**	**Control**
Fibromyalgia	10	6
Rheumatoid arthritis	1	2
Cervical nerve root impingement	0	3
Osteoarthritis	1	0
Fibromyalgia + rheumatoid arthritis	0	1
Fibromyalgia + osteoarthritis	0	1
Psoriatic arthritis	1	0
Low back pain	1	0
Ankylosing spondylitis	1	0

Self-report Measures

Questionnaires were administered once during each of the 2 experimental sessions, and were used to measure improvements in mental and physical health, the controllability and self-management of pain, sensory, and affective appraisal of clinical pain, and mindfulness. Mental and physical health outcome variables were measured using the summary scores from the Short-Form 36 health survey.[28] Improvements in the self-management of pain were assessed using the Pain Stages of Change questionnaire,[29] which is designed to measure the stages a patient goes through in their readiness to adopt a self-management approach to pain. This scale has been found to best fit a 2-factor structure: "Contemplation" of change and "Engagement" in pain self-management, which yield separate scores for each.[30] The "Engagement" subscale summarizes patients' level of acceptance of a self-management approach to chronic pain, their attempts to improve self-management skills, and continued development of those skills. We measured "perceived control over pain," using the brief version of the Survey of Pain Attitudes.[31] This subscale contains items that relate to the ability to control the actual sensation of pain (eg, "There are many times when I can influence the amount of pain I feel."), but mostly within the context of influencing pain indirectly through the ability to regulate thoughts and emotions (e.g. "Just by concentrating or relaxing I can 'take the edge' off of my pain," and "I believe that I can control how much pain I feel by changing my thoughts," and "I have noticed that if I can change my emotions I can influence my pain."). The scale therefore broadly relates to the management and regulation of pain as a multidimensional (sensory, emotional, cognitive) experience, with a focus on cognitive and emotional responding. We assessed clinical pain experience using the Short-Form McGill Pain Questionnaire,[32] which has subscales for sensory and affective pain. Mindfulness was assessed using the Mindful Attention and Awareness Scale (MAAS),[7] which mostly measures the aspect of mindfulness related to present-focused attention and acting with awareness.[6]

Neural Responses to Acute Pain

To measure treatment effects on pain processing, the options are to either measure brain responses to chronic pain

or responses to acute experimental pain. Acute experimental pain models are limited in understanding responses to chronic pain, particularly because of the difference in meaning attributed to the 2 types of pain. However, acute pain models have the advantage of being able to use a highly controllable stimulus that could be kept constant between experimental sessions separated by time. The ability to manipulate chronic pain experimentally is very challenging and likely to lead to much greater unwanted variability in the data as a result of not being able to standardize the type, quality, and intensity of pain across participants and across experimental sessions. Although the use of acute pain also has significant disadvantages, the advantages appear to outweigh these, as an experiment based on experimental manipulation of chronic pain would be even more difficult to conduct and interpret. In this study, neural activity was therefore measured relating to anticipation and experience of acute pain.

During each experimental session, subjective reports and electrophysiological responses to acute pain were assessed, using a protocol published previously (see Brown and Jones[25] for details). Briefly, acute pain was induced using a CO_2 laser stimulus that specifically activates nociceptors in the skin.[33] Heat stimuli of 150 ms duration and a beam diameter of 15 mm were applied to the dorsal surface of the participants' right forearm. Patients were not instructed to use any meditation techniques during the experiment, but were also not explicitly told not to meditate.

In the first of the 2 sessions, an initial psychophysics procedure was performed as detailed elsewhere[25] to determine a moderately painful level of laser stimulus intensity for each participant (level 7 on a 0 to 10 scale, in which 0 was equivalent to "not at all unpleasant," and 10 was equivalent to "extremely unpleasant"). This intensity was used for both sessions, and hence the laser energy did not vary between sessions. The main experiment, also detailed in a previous paper,[25] consisted of the delivery of 30 moderately painful laser pulses, each occurring after 3 visual anticipation cues (Fig. 1A). Participants were instructed to focus on the unpleasantness of the pain at all times (during pain anticipation and experience), to maximize the processing of pain in emotion-related neural networks, although we have no data to judge the extent to which this was achieved in individual patients. It was explained to participants that focusing on the unpleasantness of pain meant being aware of any unpleasant sensations in the arm that might have been there even in the absence of pain stimuli (eg, during anticipation). In response to each laser pulse, participants provided a rating of the unpleasantness using the same 0 to 10 numerical scale as used in the psychophysics testing procedure as detailed above.

EEG Recordings of Anticipatory and Pain-evoked Responses

We measured the brain's evoked response to anticipating and experiencing pain, by taking EEG recordings from 61 scalp electrodes placed according to an extended 10-20 system (EasyCap in combination with a Neuroscan system). Bandpass filters were set at DC—100 Hz, with a sampling rate of 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 were measured for off-line reduction of blink-and-eye-movement artifacts.

Analysis of Self-report Measures

There was a lack of normality in some of the self-report measures (McGill pain scores, MAAS scale) after splitting the data into groups and sessions. We found what appeared to be significant amounts of kurtosis in the McGill pain scores, caused by the presence of outliers (3 in total). The MAAS scale also had 1 outlier, but only in the control group pretreatment scores. Taking this into account as well as the relatively small sample size, we considered that nonparametric tests would result in more robust statistics, and that this was appropriate to apply to all the outcome measures. Initial analyses used nonparametric statistics with 1-tailed tests (hypothesizing a direction of change toward improvement in the MBPM group). Nonparametric repeated-measures ANOVAs were conducted (following the method of Brunner and Puri[34]) on each relevant subscale from each self-report measure, with group (intervention, control) and session (first, second) as factors. Main effects and interactions are reported for a total of 8 outcome measures. Results were considered significant after correcting the P-values using the false discovery rate (FDR) statistic set at $q = 0.05$. The resulting P-value threshold at this level was $P < 0.01$. Post hoc paired tests were performed between sessions within each group separately, using the Wilcoxon signed-rank test, and unpaired tests were also conducted between groups within each session using the Kruskal-Wallis test.

For assessing linear relationships between changes in psychological variables over time, raw change scores from each self-report measure were firstly created by subtracting scores in the first session from those in the second session. This normalized the self-report data, allowing the use of parametric statistics for further analyses. We also computed residual change scores as a more conservative approach in cases where there any correlations of raw change scores with pretreatment scores, thus controlling for any regression-to-the-mean effects. A series of regression analyses were used to test whether improvement in mental health was predicted by improvement in pain self-management and control ("engagement," "perceived control"), clinical pain symptoms, as well as increases in self-reported mindfulness, using both raw change and residual change scores. Results were considered significant after correcting the P-values in each analysis (raw change and residual change scores) separately using the FDR statistic set at $q = 0.05$. The resulting P-value thresholds at this level were $P < 0.03$ for raw change score statistics, and $P < 0.02$ for residual change score statistics.

Preprocessing of EEG Data

EEG data were analyzed using the EEGLAB toolbox (v4.515) running on MATLAB version 7.8. Preprocessing of data was performed identically to that detailed elsewhere.[25] Briefly, averaged ERPs covering the anticipation and pain phases of neural activity were created for each participant and each session, after the removal of linear trends in the data and ocular artifacts (by removing artifactual components after performing Independent Components Analysis), and filtering at 10 Hz low pass. ERPs were baseline-corrected to either the 500-ms interval preceding the visual anticipation cue (for the measurement of anticipatory-evoked responses) or the 500 ms preceding the laser stimulus (for measurement of the pain-evoked response). Data were referenced to the common average before proceeding further with data analysis.

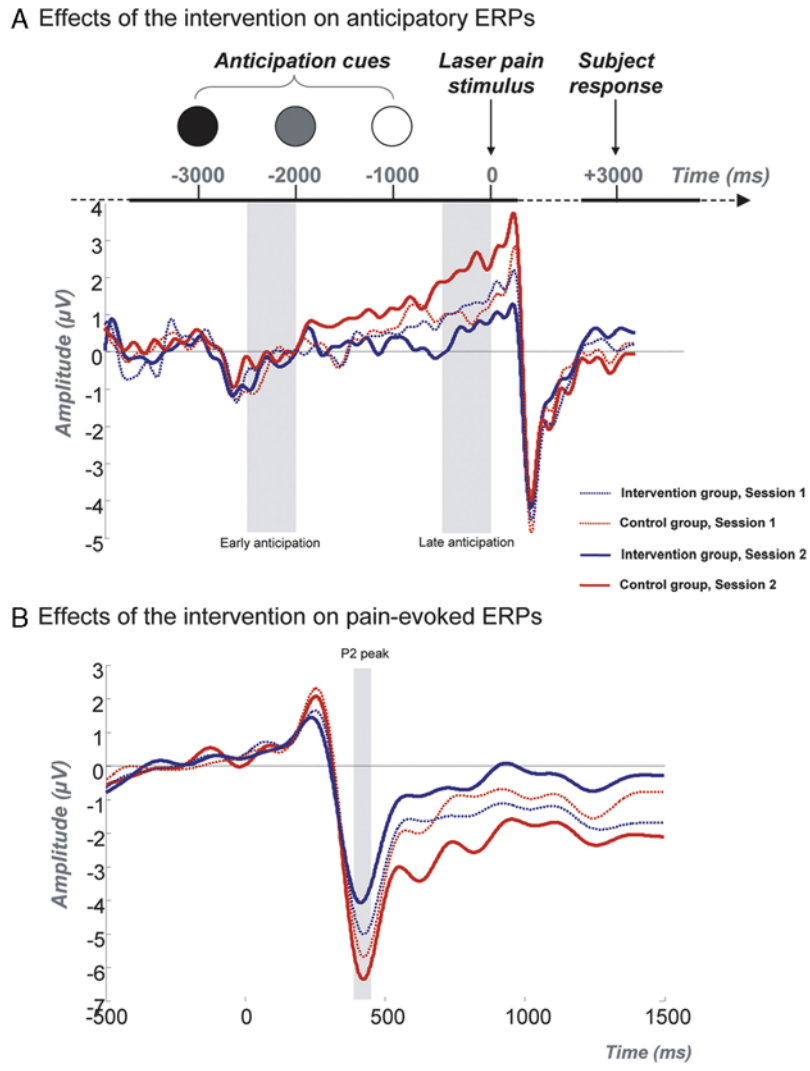

FIGURE 1. A, Effects of the intervention on the anticipation-evoked potential at electrode CPz corrected to the preanticipation baseline (−3500 to −3000 ms), with early and late anticipation periods marked that were used for further analysis. B, Effects of the intervention on the laser-evoked potential at electrode C2 after correcting to the prestimulus baseline (−500 to 0 ms).

Two 500-ms temporal periods of the anticipatory brain response were extracted for analysis: an "early" period, at −2500 to −2000 ms preceding the laser stimulus, and a "late" period, at –500 to 0 ms preceding the laser stimulus, as detailed and justified elsewhere.[25] The P2 peak of the laser-evoked potential was also analyzed. For each participant and condition, P2 peak latencies were determined at the electrode for which the P2 peak showed maximum amplitude (Cz). An averaged 20 ms window of laser-evoked potential data was then extracted, centered on this latency.

Analysis of ERP Data

For each temporal period (early anticipation, late anticipation, P2 peak), the voltage at 5 electrodes were extracted for analysis of ERP amplitudes. The 5 electrodes were those showing the peak amplitude over the whole scalp for that time window, plus 4 adjacent electrodes. For early anticipation these electrodes were POz, Oz, Pz, PO3, and PO4; for late anticipation CPz, Cz, Pz, CP1, and CP2; and for the P2 peak Cz, FCz, CPz, C1, and C2. We used a nonparametric repeated-measures ANOVA (factors: group, session) to identify main effects and interactions on the anticipatory and pain-evoked potentials. The ANOVA was performed once for each of the 3 time periods and for each of the 5 corresponding electrodes, with a total of 15 comparisons. Results were judged to be statistically significant after correcting for multiple comparisons using FDR, with a q value of 0.05. EEG data are reported using 2-tailed statistics because we did not specify a priori the direction of effects in terms of the polarity of evoked responses and magnitude of source activity.

Source Analysis of ERP Data

Sources of anticipatory and pain-evoked potentials were estimated using the imaging approach to source reconstruction as implemented in SPM8 for MEG/EEG, combined with custom MATLAB code for batch processing. The method was used as detailed elsewhere.[35] Briefly, an

8196 vertex template cortical mesh was used as a forward model, coregistered to the electrode positions of the standard 10-20 system. The lead-field of the forward model was computed using the 3-shell BEM EEG head model available in SPM8. Source estimates were computed on the canonical mesh using 256 multiple sparse priors per hemisphere[36] under group constraints.[35] Source prior smoothness was set at 1 mm. After calculating the source solution over anticipation and pain, 3-dimensional images were created from averaged activity over smaller time windows that representing the specific time window of interest, calculated with a Gaussian-weighted window [500 ms (FWHM) for early and late anticipation and 40 ms for the P2 peak] centered on the middle of the time interval. The resulting images were smoothed at 10 mm FWHM.

Statistical analysis at the group level was performed using conventional SPM t tests. To control for type I errors, statistical parametrical maps were primarily thresholded at $P_{voxel} < 0.05$ (uncorrected) using RFT on the cluster level ($P_{cluster} < 0.01$, whole-brain FWE). In cases where clusters were too small to reach this threshold but showed particularly high levels of voxel-level significance at $P_{voxel} < 0.01$ (whole-brain FDR), these results are also reported. In the first analysis, sources of brain activity activated and deactivated during each time period were determined in a series of tests on data averaged across groups in the first session only. For early anticipation, late anticipation and the P2 peak separately, sources at each time period were contrasted with sources during the baseline. In the second analysis, group × session interactions in the source activity during each time period were tested using the F statistic, with post hoc t test comparisons. The statistical model included the factors participant, group, and session. The following independence and equality of variance assumptions were used in modeling. Participant and group were assumed to be independent observations, as they were not expected to covary with each other, whereas session effects were considered not independent in that they were likely to be correlated. Participant and session were assumed to have equal error variance, whereas group was assumed to have unequal variance. This is because random allocation only guarantees equal variances of pretreatment measurements, whereas unequal variances of posttreatment measurements are often seen in clinical trials.

Analyses of Volumes of Interest (VOIs)

We extracted data from VOIs identified in the previous analyses [anticipation/pain (de)activations, and group × session interactions] as possible correlates of the self-report variables. The following analyses were performed on VOIs after subtracting activity between sessions (session 2 minus session 1), and comparing with self-report measures subtracted in the same way. The analyses were also completed on residual change scores from the above measures. Linear regression was used on the data pooled over both groups to test whether neural activity in VOIs altered by the MBPM was predictive of self-report variables. Of further interest was the question of whether neural activity in VOIs that predicted self-report variables acted as mediators of the effects of the MBPM on these variables. Using a Sobel test for mediation, results were considered significant at same level as the corresponding regression statistics (derived from FDR correction), which was $P < 0.03$ for raw changes scores and $P < 0.02$ for residual change scores.

RESULTS

Self-report Outcomes

The MBPM resulted in statistically significant improvements in mental health (Table 2). There was also improved engagement in pain self-management, and greater perceived control over pain. These secondary outcomes were significant predictors of improved mental health (Table 3).

There was a trend toward a reduction in affective clinical pain scores in the treatment group that did not reach significance in the interaction with the control group, but in post hoc tests was significant for the MBPM group without the control comparison. However, there was no significant effect of the MBPM on ratings of acute experimental pain relative to the control group (Table 2). According to the regression analyses (Table 3), improvement in mental health was not related to changes in clinical pain ratings (sensory or affective). There was no evidence of improvement in physical health in the intervention group, although there was improvement in the control group, but this was not statistically significant in the interaction with the intervention group (Table 2).

Increases in self-reported mindfulness were tested for correlations with primary and secondary outcomes variables, to provide evidence that improvement in these variables were related to specific effects of the intervention rather than nonspecific effects. Significant correlations were found between greater mindfulness and improved mental health (raw change scores: $r = 0.47$, $P < 0.01$; residual change scores: $r = 0.48$, $P < 0.01$), engagement in self-management (raw change scores: $r = 0.75$; $P < 0.001$; residual change scores: $r = 0.65$, $P < 0.001$), perceived control over pain (raw change scores: $r = 0.62$, $P < 0.001$; residual change scores: $r = 0.43$, $P < 0.02$), and affective ratings of clinical pain (raw change scores: $r = 0.44$, $P < 0.02$; residual change scores: $r = 0.41$, $P < 0.03$).

Treatment Effects on Anticipation and Pain-evoked ERPs

The MBPM and control groups showed opposite pre-to-post session effects on the anticipatory-evoked and pain-evoked ERP response, with increases in both components in the control group and decreases in both components in the intervention group (Figs. 1A and B). During late anticipation, significant group x session interactions were found at electrodes CPz ($P < 0.01$) and CP2 ($P < 0.01$), such that neural activity was decreased in the intervention group compared with the control group. During the P2 peak, significant interactions were found at electrode C2 ($P < 0.001$), with the direction of change also being a relative decrease in the intervention group compared with the control group. No significant effects were found during early anticipation at the electrodes chosen for analysis.

Sources of Anticipation and Pain-evoked ERPs

Sources of the ERPs (Supplementary Table 1 and Fig. 2A, Supplemental Digital Content 1, http://links.lww.com/CJP/A39), which showed increases relative to baseline, were as follows. During early anticipation, clusters of neural activity were increased in right anterior insular, dorsomedial prefrontal, anterior cingulate and subgenual cingulate cortices. During late anticipation, similar sources were found, but with larger contribution from bilateral clusters of sources in the medial temporal lobe and neighboring regions encompassing amygdala, putamen, anterior insula, and ventrolateral prefrontal cortex. During pain

TABLE 2. Self-report Outcome Measure Statistics: Means (SD), and *P*-Values From ANOVAs and Post Hoc Tests

	Mean (SD)							Post Hoc Tests			
	Intervention Group		Control Group		Main Effects			Session Effect		Group Effect	
	Session 1	Session 2	Session 1	Session 2	Group	Session	Interaction	Intervention	Control	Session 1	Session 2
Short-Form 36 Health Survey											
Mental Health	58.4 (15.6)	75.3 (10.4)	61.5 (14.4)	58.2 (17.8)	0.08	*0.01*	*0.00*	*0.01*	0.15	0.31	0.02
Physical Health	143.3 (86.4)	139.8 (82.6)	136.0 (56.1)	172.6 (67.1)	0.22	0.08	0.08	0.31	0.02	0.31	0.17
Pain Stages of Change Questionnaire (PSOCQ)											
Engagement	20.0 (11.9)	37.9 (9.1)	21.5 (17.0)	23.6 (15.9)	0.09	*0.00*	*0.00*	*0.00*	0.14	0.43	*0.01*
Contemplation	40.0 (4.4)	40.1 (6.1)	39.0 (6.1)	38.7 (5.9)	0.12	0.44	0.49	0.43	0.26	0.11	0.18
Survey of Pain Attitudes Questionnaire											
Perceived control over pain	10.5 (3.5)	14.1 (2.5)	11.0 (3.6)	10.8 (4.6)	0.09	*0.01*	*0.01*	*0.01*	0.47	0.47	0.02
Short-Form McGill Pain Questionnaire											
Sensory pain	18.4 (5.8)	17.6 (7.1)	20.2 (6.6)	18.6 (7.1)	0.31	0.17	0.38	0.45	0.10	0.33	0.35
Affective pain	6.2 (3.7)	4.3 (2.6)	4.4 (3.8)	4.6 (4.3)	0.20	0.13	0.13	*0.01*	0.38	0.10	0.38
Laser pain unpleasantness ratings	5.4 (2.0)	5.9 (1.9)	5.9 (1.3)	6.3 (1.3)	0.19	0.18	0.42	0.35	0.18	0.17	0.32
Mindful Attention and Awareness Scale	58.5 (14.2)	68.4 (9.5)	58.3 (11.5)	57.5 (13.8)	0.09	0.04	*0.00*	*0.01*	0.45	0.47	*0.01*

Value in italics are statistically significant.

processing (P2 peak), there were significant bilateral medial temporal sources similar to those observed during late anticipation, with the addition of a large cluster encompassing mid-anterior cingulate cortex, extending to superior frontal and parietal regions including the supplementary motor area.

Sources of ERPs showing deactivations relative to baseline (Supplementary Table 1 and Fig. 2B, Supplemental Digital Content 1, http://links.lww.com/CJP/A39) common to all time periods, were the left and right DLPFCs. During early anticipation, additional deactivations were centered on right secondary somatosensory cortex (S2) cortex and the neighboring opercular-insular regions, and areas of the middle occipital cortex and cuneus. During pain, additional deactivations were in a region encompassing areas of the posterior cingulate cortex and precuneus, and in medial prefrontal cortex.

Treatment Effects on Sources of Anticipation and Pain-evoked ERPs

Group × session interaction effects on the ERP sources were identified (Supplementary Table 1 and Fig. 2C, Supplemental Digital Content 1, http://links.lww.com/CJP/A39). Notably, the regions that were significantly activated beyond baseline were not affected by the intervention. Rather, regions showing decreases in activity relative to baseline were affected. During early anticipation, clusters were significantly changed in the left and right DLPFCs, and in right S2 cortex. The right DLPFC cluster extended into the right posterior insula/S2 cortex. Post hoc analyses revealed these regions to be decreased to a lesser extent in the intervention group relative to the control group from session 1 to session 2. During late anticipation interactions were found in ventromedial prefrontal and supplementary motor cortices, which were decreased to a greater extent in the intervention group. During the pain-evoked ERP, there was a significant interaction in a cluster including the left amygdala and anterior insula, which showed both a nonsignificant decrease in the intervention group and a larger increase in the control group.

Neural Correlates of Self-report Outcome Variables

Improvements in mental health were significantly predicted by less of a decrease in activity in left DLPFC and right S2 cortex during early anticipation of pain (Table 3 and Fig. 2D). However, while these regions showed a trend toward mediating the effects of the MBPM on mental health outcomes, the analyses did not reach statistical significance (using raw change scores: $P < 0.04$ for S2 cortex and $P < 0.07$ for left DLPFC; using residual change scores: $P < 0.09$ for S2 cortex and $P < 0.14$ for left DLPFC). Left and right DLPFC and right S2 during early anticipation were also tested as predictors of self-management outcomes (Table 3 and Fig. 2D). Left DLPFC and right S2 were strong predictors of perceived control over pain. Again, left DLPFC (but not right S2) showed a trend toward mediating the effects of the MBPM on perceived control, but the effect was not significant ($P < 0.05$ for raw change scores, $P < 0.06$ for residual change scores).

DISCUSSION

The results of this study show that improvements in the mental health of patients with musculoskeletal pain as a result of mindfulness training are related to improved perceived control and engagement in self-management of pain, but not a reduction in pain symptoms. There was only a small reduction in affective ratings of clinical pain as a

TABLE 3. Regression Analyses of Self-report Outcomes and Their Neural Correlates

		Raw Change Scores				Residual Change Scores			
Dependent Variables	**Independent Variables**	**β**	***t*-Value**	***P*-Value**	R^2	**β**	***t*-Value**	***P*-Value**	R^2
Self-report outcomes									
Mental health	Engagement	0.51	3.03	*0.00*	0.26	0.52	3.08	*0.00*	0.27
	Perceived control	0.46	2.58	*0.01*	0.21	0.46	2.67	*0.01*	0.22
	Sensory clinical pain	0.07	0.35	0.36	0.00	0.02	0.11	0.46	0.00
	Affective clinical pain	−0.26	−1.36	0.09	0.07	0.26	1.38	0.09	0.07
Neural correlates of self-report outcomes									
Mental health	Left DLPFC	0.44	2.49	*0.01*	0.19	0.40	2.22	*0.02*	0.16
	Right DLPFC	0.42	2.39	*0.01*	0.18	0.25	1.33	0.10	0.06
	Right S2	0.49	2.84	*0.00*	0.24	0.51	3.01	*0.00*	0.26
Engagement	Left DLPFC	0.37	2.00	*0.03*	0.13	0.42	2.35	*0.01*	0.17
	Right DLPFC	0.20	1.05	0.15	0.04	0.30	1.62	0.06	0.09
	Right S2	0.39	2.19	*0.02*	0.16	0.55	3.34	*0.00*	0.30
Perceived control	Left DLPFC	0.50	2.91	*0.00*	0.25	0.48	2.78	*0.00*	0.23
	Right DLPFC	0.20	1.06	0.15	0.04	0.19	1.01	0.16	0.04
	Right S2	0.47	2.72	*0.01*	0.22	0.43	2.45	*0.01*	0.19

Value in italics are statistically significant.
DLPFC indicates dorsolateral prefrontal cortex; S2, secondary somatosensory cortex.

result of the treatment, while there was no effect of the treatment on ratings of acute experimental pain, and neither related to mental health outcomes. Changes in neural activity were observed such that mindfulness training reduced deactivation (ie, increased activation) of central executive regions of the brain (particularly, bilateral DLPFC) during anticipation of acute pain, without affecting regions that normally correlate with pain intensity such as the cingulate and posterior insula cortices. There were mild reductions in emotional processing regions including the amygdala and anterior insula, but improvements in psychological outcomes (mental health, perceived control, and engagement in pain self-management) were rather related to the greater anticipatory processing in DLPFC and somatosensory cortices.

Self-report Outcomes

As expected, the self-reported mental health of patients enrolled in the MBPM improved as a result of the intervention. The MBPM also increased patient perceptions that their pain was controllable and manageable, effects that correlated with the improvements in mental health, without a significant reduction in clinical pain symptoms. Although there was evidence of a reduction in affective ratings of clinical pain within the MBPM group, this effect did not reach significance relative to the control group, and was not related to improvements in mental health. Hence, within 2 weeks post-intervention, mental health was more closely related to the perception of pain as being manageable than a reduction in pain symptoms. This is consistent with the aims of mindfulness meditation, which are to improve the ability to regulate and self-manage the response to pain rather than the sensation of pain. This highlights that fact that the term "perceived control over pain" needs to be interpreted within a broader biopsychosocial context than simply control over pain sensation. Perceived control can have different meanings depending on whether it is the sensory aspects of the pain or broader emotional/behavioral aspects and responses to the pain that are perceived as being better managed.

This study was not a clinical trial of the intervention, but rather an investigation of *how* the intervention exerts beneficial effects on mental health in patients with chronic pain. Yet, the lack of an active control group, as would be used in a clinical trial to control for placebo effects, is a limitation of the design. This means we cannot discount a number of possible influences on the MBPM group results that are known to contribute to placebo effects, including patient expectations, therapist attention and group social support. Other limitations include that the ratio of females to males was higher in the intervention group, and that we did not measure education level and pain duration, which may have been unbalanced in the 2 groups and possibly may have affected the study outcomes. Although these are valid concerns, the current data showing relationships between the main outcomes of interest and the outcomes from the mindfulness scale encourage an optimistic view of the results. Self-reported mindfulness was found to correlate with improvements in mental health and pain self-management outcomes, as well as reductions in affective ratings of clinical pain. The data provide assurance that improvements in the main outcomes of the study were related to the specific psychological processes targeted by the intervention, although further work is warranted to more robustly control for possible placebo effects. These data also confirm previous reports[8,37] that mindfulness is related to emotional functioning in patients, and suggests that mindfulness may empower patients to manage their symptoms better.

On a note of caution, any research study, including the present study, which relies on patients' subjective reports of their pain and responses to pain, assumes that patients have paid adequate attention to their subjective states to be able to provide accurate reports. Such assessments may be measuring patient beliefs and desires about their experiences rather than the actual lived experiences. It therefore follows that we cannot determine for certain whether participants were attending to pain unpleasantness during the experimental pain procedure, and we settled for asking for ratings of unpleasantness ratings on a 0 to 10 pain scale as a way of encouraging attention to pain unpleasantness and accurate reporting. It may have been potentially useful to debrief patients after the experiment to find out what they were attending to during the experiment, to see whether they were able to engage with that task, although this also suffers the limitation of being a better gauge of patients'

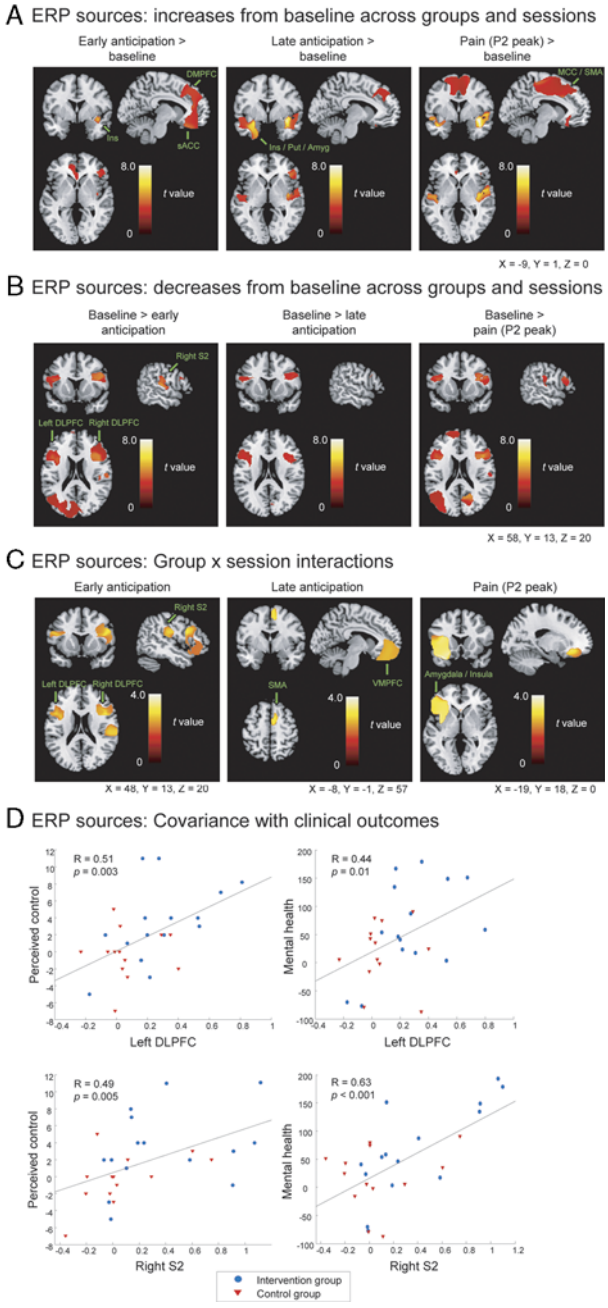

FIGURE 2. ERP sources showing (A) increases and (B) decreases relative to the preanticipation baseline from session one, averaged across both groups. C, Brain regions showing significant effects in the group × session interaction. D, Neural activity predicting scores on self-report outcome measures (subtracted scores: session 2 minus session 1). Amyg indicates amygdala; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; Ins, insula; MCC, midcingulate cortex; Put, putamen; sACC, subgenual anterior cingulate cortex; SMA, supplementary motor area; S2, secondary somatosensory cortex; VMPFC, ventromedial prefrontal cortex.

beliefs or desires than an accurate measure of engagement. These limitations would benefit from more objective measurement of responses to pain, and is one justification for the use of neurobiological indicators of pain in this study.

Electrophysiological Outcomes

One aim of this study was to improve our understanding of the neurobiological changes associated improvements in pain responding. In this study we used acute experimental laser pain as a proxy for patient's clinical pain, which had the advantage of being able to separate out anticipatory activity (related to expectations and beliefs) from pain-evoked activity, but the disadvantage of having a different meaning to the patient (likely being less distressing) than their clinical pain. The EEG results showed that, as expected, the DLPFCs were modified by mindfulness training. Unexpectedly, changes were also found in S2 cortex. These regions were normally deactivated during early pain anticipation in both intervention and control groups. The effect of the MBPM was to cause DLPFC and S2 cortex to be less deactivated during the early phase of anticipation than normal. Effectively, the intervention stabilized activity in these regions so that they were less affected by the anticipation of pain.

The meaning of the reduced deactivation, rather than simply activation, requires careful interpretation. Deactivations occurring due to task-related demands are normally associated with the "default mode" network, involved with internal mentation or "daydreaming," which is considered to include the medial temporal lobes, posterior cingulate cortex, and medial prefrontal cortex.[38–40] The posterior cingulate and medial prefrontal cortices were indeed deactivated in this study across groups and sessions during the pain response, but not during anticipation. But the regions of interest, DLPFC and S2, are not considered part of the default mode network. Rather, DLPFC is considered part of an executive network that is anti-correlated with default mode brain regions,[38,41] whereas S2 cortex activates in response to task-related demands to process somatosensory information, including pain.[42,43] Reduced deactivation of these regions could therefore indicate the maintenance of cognitive control and task-related processing of somatosensory information during anticipation of pain. This interpretation is consistent with the component of mindfulness training involving learning to maintain present-focused attention, particularly on body sensations, even during difficult experiences such as pain that may encourage a more distracted mental state as a coping strategy. Indeed, increases in DLPFC and S2 activity have been shown to occur during states of mindfulness meditation.[19,21] Further, activation of these regions occurs in individuals without previous mindfulness training who are given instructions to pay attention "mindfully", that is, with a present-focus on the raw sensory experience, rather than thinking *about* the experience in a more mentally distracted, or ruminative, way.[44]

Because mindful present-focus reduces rumination on emotional experiences, it can be considered an emotional regulation strategy. The DLPFC has been shown to activate when participants are asked to re-appraise emotional stimuli by focusing on non-emotional aspects of the experience.[23,45,46] The DLPFC is thought to be important for emotional regulation by inhibiting conditioned emotional responses,[22] in association with reductions in neural activity in the insula and amygdala.[47] These interactions are thought to dampen the affective response to pain.[47,48] This is consistent with the findings from this study that the MBPM group showed a small reduction in affective pain ratings (although not significant in the interaction between group and session), whereas sensory pain ratings remained unchanged. In addition, during late anticipation, the MBPM either decreased or

prevented an increase in neural activity in regions including the amygdala, anterior insula, and ventromedial prefrontal cortex. These regions have previously associated with conditioned fear and anticipatory anxiety.[49–51] The results from the present study, combined with the results from previous work, are consistent with the hypothesis that mindfulness recruits the cognitive control mechanisms of DLPFC. This region was related to the improvements in mental health in our study, consistent with their known role in regulating emotional responses. However, we were not able to demonstrate a mediatory role for DLPFC in the therapeutic outcomes; indeed any such analysis would be based on correlative relationships that cannot prove causation without specific manipulation of the brain regions involved.

Interestingly, S2 cortex activity during early anticipation of pain also predicted improvements in mental health and measures of pain control and self-management. This finding might appear curious as S2 cortex is not considered a region involved with emotional regulation or other aspects of cognitive control. S2 cortex does activate during anticipation of pain,[25] an effect that may be related to expectancy of pain,[52,53] which normally modulates the subsequent pain experience.[54] However, expectancy effects normally co-occur with activation in other regions such as the cingulate and insula cortices,[52,53] which we did not observe, nor did we see a change in acute experimental pain perception. A more likely explanation than a change in expectancy, which would be consistent with the aims and practices of mindfulness meditation, is that greater S2 activity resulted from a greater tendency after mindfulness training to attend to the quality of body sensations. It is an open question as to whether this region is involved in the regulation of cognition and emotion. We speculate that its greater activity during anticipation of pain after mindfulness training is more likely to be a consequence of greater emotional regulatory processes taking place elsewhere, for example in higher-order brain regions such as DLPFC. The strong correlations of increased activity in S2 cortex with outcome measures including mental health suggests that this greater S2 cortex activity may turn out to be a useful surrogate of improved emotional regulation resulting from meditative concentration on body sensations, but we cannot at present consider it causally related.

Although early anticipatory DLPFC and S2 activity had clear correlates with pain self-management/control and mental health, additional findings of interactions between session and group factors during late anticipation in ventromedial prefrontal cortex and supplementary motor area did not have such correlates. These interactions resulted from both decreases in the intervention group *and* increases in the control group, and explain well the observed effects on the amplitude of the anticipatory potential during late anticipation, which was increased in the control group and decreased in the intervention group. Further effects were also found in the control group: during the experience of acute laser pain (P2 peak), interactions between group and session were observed in a cluster including the amygdala and anterior insular cortex, which resulted from increases in the control group when there was no change in the intervention group. These results were also not related to self-report outcomes. It is possible that the increased brain activity during both anticipation and pain in the control group could be caused by fear conditioning toward the experimental procedure. In other words, conditioned fear may augment the neural processes of negative expectancy, thereby affecting the processing of the pain stimuli. Previous studies have shown amygdala and anterior insular cortex in particular to be part of a network that develops conditioned fear responses to stimuli, including pain stimuli.[49,55–57] We speculate that control group participants may have more fearfully anticipated the pain stimuli in the second session having attended the first session a number of weeks earlier, an effect that appears to be absent in the MBPM group.

However, a limitation of this study is that acute pain in an experimental setting, where pain induction is very brief and episodic, could be considered very different from the characteristics of chronic pain, likely resulting in different response patterns. Although there are significant advantages to the use of acute pain models for this type of study, namely the ability to keep pain constant between 2 experimental sessions, there is a possibility that the treatment outcome results from this study are in fact not causally related to the effects shown of mindfulness training on acute pain responding. However, we do know that experimental pain and ongoing clinical pain are processed within the same structures within the pain matrix.[58] Although there is greater processing of clinical pain within the medial pain system during clinical pain consistent with its greater emotional salience,[58] it is difficult to imagine that entirely different control processes are operating during the different types of pain. Despite this, we would suggest caution in drawing causal attribution from the current results which should be interpreted as purely correlational at this stage.

Relationship to Previous Studies

The results of this study can be contrasted with other published experimental data showing effects of mindfulness meditation on pain perception and processing. Our previous study[25] used the same experimental protocol, except that we studied, in a single session, a group of healthy participants with a range of past experience in meditation. Meditation experience was associated with lower perceived pain unpleasantness and related neural processing of pain anticipation in the cingulate cortex, with less subsequent pain processing in the insula. Other studies investigating relationships between meditation expertise (in advanced practitioners) and pain processing have also shown that meditation is associated with less processing in regions such as insula and ACC.[59,60] In the current study, the MBPM group showed lower affective ratings of clinical pain after treatment but this did not reach significance in the interaction between group and session. We also found no evidence of a reduction in neural processes within pain intensity processing regions such as insula and cingulate cortex after the MBPM. Previous studies of advanced meditation practitioners have also shown increases in S2 cortex activity[60] and increased gray matter in S2 cortex that correlates with lower pain sensitivity.[61] This is consistent with our findings of increased anticipatory activity in S2 cortex after mindfulness training.

It is possible that significant reductions in activity in pain intensity-related brain regions such as the cingulate and insula cortices only may become observable with longer training than took place in this study, as the reduction in anticipatory pain processing in our previous study was most apparent in participants with years of meditation experience.[25] A reduction in pain may therefore only occur secondarily to improvements in mental health, and over a longer time scale. This conclusion may appear to be inconsistent with research by other groups[62,63] that have

shown effects of meditation training on reduced pain perception and neural processing of pain in healthy participants after only very short-term training of a few days. However, our experimental approach differed in that we measured neural activity in patients with chronic pain, and while they focused on the unpleasantness of the experienced pain rather than asking them to withdraw attention toward an object of meditation, as was done in the research showing significant short-term effects.[62,63] We therefore suspect that our results are more reflective of long-term (trait) changes in pain processing that are not dependent on temporary states of meditation, although this must be considered speculation at this point.

CONCLUSIONS

The study supports the hypothesis that mindfulness training provides a cognitive strategy for improving pain management, which has positive consequences for mental health. Our results show that this is related to maintaining activity in central executive regions responsible for emotional regulation (DLPFC) during anticipation of pain, whereas reductions in processing during pain experience were modest and restricted to regions that are known to mediate emotional responses to pain including the amygdala and anterior insula. Although the effects on neural activity were measured in relation to acute pain, the effects were related to clinical outcomes, suggesting that the acute pain model may be useful for understanding the effects of mindfulness training on neural activity related to pain management. However, the longer-term effects of mindfulness training on clinical pain or its management cannot be determined from this study, nor is it clear the extent to which the current results include effects related to placebo. We consider that this study provides some valuable insights into short-term functional changes pain processing related to improvement in mental health. Further studies are required with longer follow-up periods to understand the potential long-term effects of mindfulness training on neural networks related to cognitive control and emotional regulation, and with placebo controls to help distinguish therapy-specific effects on nociceptive processing from those of placebo.

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