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Disrupted Brain Circuitry for Pain-Related Reward/Punishment in Fibromyalgia

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Objective. **While patients with fibromyalgia (FM) are known to exhibit hyperalgesia, the central mechanisms contributing to this altered pain processing are not fully understood. This study was undertaken to investigate potential dysregulation of the neural circuitry underlying cognitive and hedonic aspects of the subjective experience of pain, such as anticipation of pain and anticipation of pain relief.**

Methods. **Thirty-one FM patients and 14 controls underwent functional magnetic resonance imaging, while receiving cuff pressure pain stimuli on the leg calibrated to elicit a pain rating of ~50 on a 100-point scale. During the scan, subjects also received visual cues informing them of the impending onset of pain (pain anticipation) and the impending offset of pain (relief anticipation).**

Results. **Patients exhibited less robust activation during both anticipation of pain and anticipation of relief within regions of the brain commonly thought to be involved in sensory, affective, cognitive, and pain-modulatory processes. In healthy controls, direct searches and region-of-interest analyses of the ventral tegmental area revealed a pattern of activity compatible with the encoding of punishment signals: activation during anticipation of pain and pain stimulation, but deactivation during anticipation of pain relief. In FM patients, however, activity in the ventral tegmental area during periods of pain and periods of anticipation (of both pain and relief) was dramatically reduced or abolished.**

Conclusion. **FM patients exhibit disrupted brain responses to reward/punishment. The ventral tegmental area is a source of reward-linked dopaminergic/γ-aminobutyric acid–releasing (GABAergic) neurotransmission in the brain, and our observations are compatible with reports of altered dopaminergic/GABAergic neurotransmission in FM. Reduced reward/punishment signaling in FM may be related to the augmented central processing of pain and reduced efficacy of opioid treatments in these patients.**

Fibromyalgia (FM) is a chronic, relatively common pain disorder characterized by persistent, widespread body pain and myofascial tenderness, and it is considered the quintessential functional pain disorder. The prevalence of FM in the general US population is estimated to be 3.4% in women and 0.5% in men, and it increases with age (reaching >7% in women between ages 60 and 79 years) (1). Some of the hallmarks of FM include alterations of pain-modulatory processes in the central nervous system, a prominent role of negative affective factors in maintaining pain and disability, and a poor enduring response to peripheral treatments such as topical agents or trigger point injections, as well as opioids (2). These characteristics highlight the central nature of FM pathophysiology and have been the basis for several brain imaging studies of this disorder. Collectively, evidence derived from psychophysical and functional neuroimaging studies supports the notion of

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augmented sensitivity to painful stimulation in FM, which is thought to be due predominantly to aberrant brain processing of pain-related information (2,3).

However, while the neural correlates of experimental pain (4–6) and clinical pain (7) in FM have been the subject of several investigations, potential dysregulation of the neural mechanisms underlying anticipation of pain and anticipation of pain relief in this population of patients with chronic pain has received little attention. This is an important distinction, since cognitive, motivational, and affective processes have been shown to be intimately involved in the perception and reporting of pain, including in patients with FM (3,8,9). Importantly, the state of the brain preceding painful stimulation has been shown to predict responses to experimental pain (10), as well as clinical pain (11). Expectancy and pain-relevant anxiety, in particular, have been shown to shape subsequent perceptual states (12). Relief from pain, on the other hand, is a positive hedonic experience intrinsically linked to pain (13). It has been suggested that the experience of relief may be altered in patients with chronic pain (14). Since pain and the anticipation of both pain and relief have strong hedonic value linked to their punishment/reward properties, it is reasonable to suspect that these states may be processed differently in FM patients, particularly in structures involved in the encoding of appetitive or aversive stimuli.

In the present study of FM patients and controls, we used functional magnetic resonance imaging (fMRI) and cuff pain algometry to investigate brain responses to deep tissue noxious stimulation, as well as responses to anticipation of pain and anticipation of relief. We adopted both a whole-brain approach and a region-of-interest (ROI) approach focused on the nucleus accumbens and the ventral tegmental area, two mesolimbic structures known to be involved in the processing of reward/punishment (15) and implicated in FM pathophysiology in positron emission tomography (PET) studies (16,17).

PATIENTS AND METHODS

Subjects. Thirty-one FM patients and 14 healthy controls were recruited to participate in this study. Enrolled patients were diagnosed as having fibromyalgia (as confirmed by physician and medical records) and met the recently proposed American College of Rheumatology criteria (18), which require the presence of widespread pain as well as a number of somatic and cognitive symptoms. Healthy controls were free of chronic pain and rheumatic disease. For both groups, exclusion criteria included age <18 years, history of significant psychiatric, neurologic, or cardiovascular disorders or current diagnosis of the same, history of significant head injury, current treatment with opioids, implanted medical or metallic objects, and pregnancy. This study was approved by the Partners Human Research Committee, and written informed consent was obtained from all participants.

Study overview. Subjects participated in two separate study visits on different days: a training visit (behavioral only) and an imaging visit. The training session was used to familiarize subjects with the stimuli and rating procedures and to determine appropriate stimulus intensities to be used during the subsequent imaging session.

Painful stimulation was achieved via cuff pain algometry. We chose this technique over other more commonly used methods of pain stimulation (e.g., contact heat) because cuff pain stimuli appear to have a preferential effect on deep tissue nociceptors (19). Since most clinical pain originates in deep tissue rather than in cutaneous receptors, investigating brain responses to deep tissue pain may prove to be more clinically relevant than investigating brain responses to evoked cutaneous pain. As in our previous studies (20,21), mechanical stimuli were delivered to the right calf using a 13.5-cm–wide Velcro-adjusted pressure cuff, connected to a rapid cuff inflator (E20 AG101; Hokanson). The cuff inflator was adapted to ramp up gradually to the target pressure over $\sim$2 seconds to minimize abrupt motion in the subject.

After completing questionnaires (including the Beck Depression Inventory, fatigue visual analog scale [VAS], Widespread Pain Index, Short Form 36 health survey, and Brief Pain Inventory), subjects were familiarized with the procedures for cuff pain algometry. Subjects sat comfortably on a chair with the left foot resting on a support at a slightly elevated position. The vascular cuff was then secured around the left gastrocnemius muscle. Quantitative sensory testing began by inflating the cuff to 60 mm Hg of pressure and making adjustments in 10–mm Hg increments until a pain intensity rating of $\sim$50 on a 100-point scale was first obtained.

During the imaging visit, ratings of intensity and unpleasantness of clinical pain (based on a VAS scale of 0–100) were obtained from patients. The stimulus pressure was briefly recalibrated prior to scanning, using procedures similar to those adopted during the training session. During a single functional imaging scan run, brain activity was investigated using blood oxygen level–dependent (BOLD) fMRI, while the patient received 3 separate tonic cuff pain stimuli (of 46–74 seconds each) set to elicit the same pain intensity level ($\sim$50 on a 100-point scale) (Figure 1A).

Prior to each cuff inflation, a cross projected in the subjects' visual field changed from black to green to signal the period of pain anticipation, and then turned black again at stimulus onset. Prior to cuff deflation, the cross switched in color from black to blue to signal the period of relief anticipation, and then turned black again at cuff stimulus offset. These visual cues appeared for 6–12 seconds (i.e., jittered in time). The use of relatively long pain stimuli was chosen to maximize the emotional responses associated with expectancy of pain and relief, and to ensure temporal separation between regressors in the design matrix. For each of the 3 pain blocks, 8 seconds after stimulus offset, subjects used a magnetic resonance–compatible button box to rate the intensity and unpleasantness of the cuff pain stimuli on 0–100 electronic scales (ePrime; Psychology Software Tools).

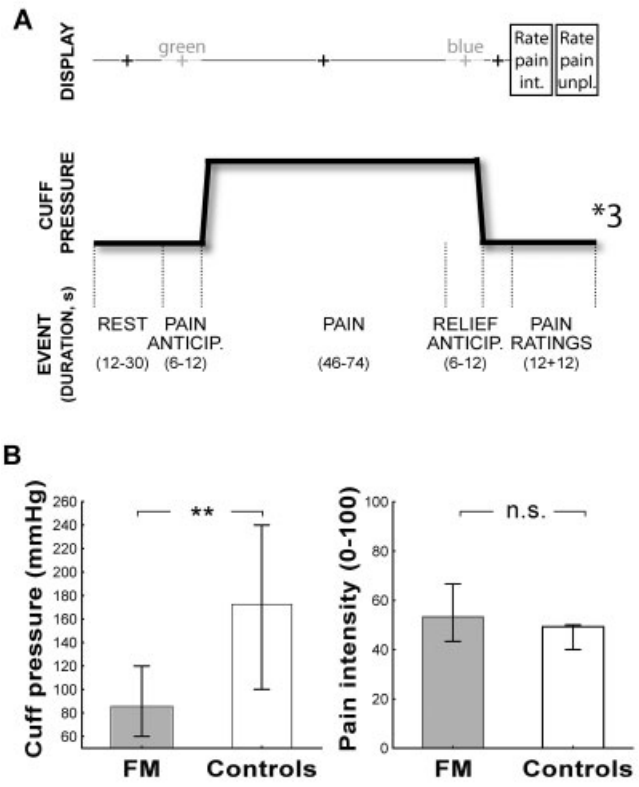

Figure 1. A, Experimental design of the study. Each patient with fibromyalgia (FM) and each control subject underwent cuff pain stimuli 3 times, while brain response was recorded using functional magnetic resonance imaging. Ratings of pain intensity (int.) and pain unpleasantness (unpl.) were obtained from patients. A cross projected in the subjects' visual field changed from black to green to signal the period of pain anticipation (anticip.). The cross switched from black to blue to signal the period of pain relief anticipation. **B,** Cuff pressure needed to induce the target pain rating (left) and pain intensity rating (right). Values are the median and interquartile range. ** = $P < 0.01$. NS = not significant.

Data from fMRI were acquired using a 3T Tim Trio MRI system (Siemens) equipped for echo-planar imaging with a 32-channel head coil. A whole brain T2*-weighted gradient-echo BOLD echo-planar imaging pulse sequence was used (repetition time [TR] 2 seconds, echo time [TE] 30 msec, flip angle 90°, 32 anterior commissure–posterior commissure–aligned axial slices, voxel size 3.1 × 3.1 × 4 mm). We also collected anatomic data, using a multi-echo magnetization-prepared rapid gradient-echo pulse sequence (TR 2,530 msec; TE 1.64 msec, 3.5 msec, 5.36 msec, and 7.22 msec; flip angle 7°; voxel size 1 mm [isotropic]).

Data analysis. All statistical analyses for behavioral data were performed using Statistica 10.0 (StatSoft), with an alpha level of 0.05. The significance of differences in the distribution of the sexes between groups was assessed using Fisher's exact test. Deviation from normal was assessed using the Kolmogorov-Smirnov test for all variables of interest: cuff pressure values (i.e., pressure values, expressed as millimeters of mercury, eliciting the target pain intensity rating of ~50 on a 100-point scale in the recalibration performed at the beginning of the imaging visit) and mean intensity and unpleasantness ratings (averaged over 3 trials). Since distribution of cuff pressure values in both patients and controls and distribution of pain intensity ratings in controls significantly deviated from normal ($P < 0.05$), all group comparisons were performed using the nonparametric Mann-Whitney U test. Group analyses were performed to compare cuff pressure values (to determine differences in pain sensitivity between FM patients and controls) and pain ratings (to assess successful calibration of cuff pressure and possible differences in the affective responses associated with the stimulus) for both pain intensity and unpleasantness separately, averaged across the 3 trials.

Functional MRI data were processed using FMRI Expert Analysis Tool version 5.98, which is part of Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) (online at www.fmrib.ox.ac.uk/fsl) (22). Data underwent the following preprocessing: motion correction, field map–based echo-planar imaging unwarping, nonbrain removal, spatial smoothing (full-width half-maximum of 5 mm), grand mean intensity normalization by a single multiplicative factor, and high-pass temporal filtering (Gaussian-weighted least-squares straight-line fitting [σ = 72 seconds]). Time-series statistical analysis was performed using FMRIB's Improved Linear Model with local autocorrelation correction. Cortical surface reconstruction (23) was performed using FreeSurfer software (online at http://surfer.nmr.mgh.harvard.edu/) for improved structural/functional coregistration purposes. A recently developed automated boundary-based registration algorithm (FreeSurfer's bbregister tool) was used for coregistration. Scans were registered to the Montreal Neurological Institute (MNI) template MNI152 standard space using FMRIB's Linear Image Registration Tool.

Our first-level within-subject general linear model analysis included the pain expectancy cue, cuff pain stimulus application, and the expectancy of pain relief cue as regressors of interest. We also modeled the period between stimulus offset and the rating periods, as well as the rating periods, as regressors of no interest. A canonical double-gamma hemodynamic response function was adopted. Parameter estimates and relative variances for each explanatory variable were then included in mixed-effects group level analyses, performed using FMRIB's Local Analysis of Mixed Effects 1+2, with enabled automatic outlier detection. Whole-brain statistical parametric maps were computed for the following regressors: pain anticipation, pain stimulus, and relief anticipation. Thresholds were set for all maps using clusters determined using a voxelwise threshold ($Z > 2.3$) and a (corrected) cluster significance threshold ($P = 0.05$).

Group comparisons of brain responses to pain anticipation, pain, and relief anticipation were also performed with a direct search restricted to the nucleus accumbens and the ventral tegmental area. Direct searches of the nucleus accumbens were performed within the labels from the Harvard–Oxford Subcortical Structural Atlas (online at http://www.cma.mgh.harvard.edu/fsl_atlas.html), and threshold was set at a (arbitrary) value of 80 (size of the right nucleus accumbens mask 11 voxels; size of the left nucleus accumbens mask 14 voxels) (data available upon request from the corresponding author). The direct search of the ventral tegmental

area was performed within an anatomically defined mask manually drawn on the MNI152 brain at a resolution of 0.5 mm, based on its location medial to the substantia nigra and the red nuclei (size of the right ventral tegmental area 77 voxels; size of the left ventral tegmental area 81 voxels) (24). The correct coregistration between each of these masks and each subject's spatially normalized fMRI maps was confirmed by visual inspection. These direct searches were performed with an uncorrected threshold value ($Z = 2.58$) and a minimum cluster size (5 voxels). From these regions, mean Z statistic values were extracted to create correlational plots, as well as to display group differences (for illustrative purposes). In order to further corroborate the significant results obtained from the ventral tegmental area direct searches, an ROI analysis was performed by averaging the Z score from all the voxels within the ventral tegmental area mask (split into left and right). An unpaired *t*-test with an alpha level of 0.05 was performed to compare average ventral tegmental area Z scores across groups, Statistica 10.0.

RESULTS

Psychophysical results. Demographic and clinical data are presented in Table 1. There was no statistically significant between-group difference for sex distribution ($P = 0.23$). Prior to scanning, FM patients reported the intensity of their current clinical pain as a mean ± SD of 34.3 ± 25.19 on a 100-point scale (range 0–78) and unpleasantness of their pain as 32.3 ± 26.7 (range 0–90). Ratings of intensity and unpleasantness of clinical pain were highly correlated ($r = 0.88$, $P < 0.0001$). In patients, baseline clinical pain ratings tended to be negatively correlated with cuff pressure values that were selected to elicit a target rating of 50 on a 100-point scale (clinical pain intensity [$r = -0.33$, $P = 0.071$], clinical pain unpleasantness [$r = -0.35$, $P = 0.051$]). As shown in Figure 1B, there was no statistically significant difference between FM patients and controls in the pain intensity ratings elicited by the cuff pressure (and the same was observed for the unpleasantness ratings) (all $P \geq 0.30$). This was expected due to percept-matched calibration. However, the pressure needed to induce the target pain rating was significantly lower in FM patients than in controls ($P < 0.01$).

Imaging results—whole brain analyses. In both groups the pain anticipation cue (Figure 2 and Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38191/abstract) elicited activation in multiple regions of the brain, including the primary somatosensory and motor cortices, the supplementary motor area, the dorsolateral prefrontal cortex, the secondary somatosensory cortex, the posterior cingulate cortex, the middle cingulate cortex, the subgenual anterior cingulate cortex, the superior parietal lobule, the insula/frontal operculum, the periaqueductal gray, the basal ganglia, the medial and lateral visual areas, the parahippocampal gyrus, and the cerebellum. Control subjects experienced significantly stronger brain responses to pain anticipation in several of these regions, including the supplementary motor area, the middle cingulate cortex, the posterior cingulate cortex, the periaqueductal gray, the ventral tegmental area and visual cortices bilaterally, the caudate nucleus (head) and the globus pallidus on the left, and the secondary somatosensory cortex and posterior insula on the right. Patients did not exhibit a stronger BOLD response to pain anticipation in any region compared to controls.

In both groups, cuff pain stimuli evoked brain activity changes in regions frequently observed as activated or deactivated during experimental pain (Figure 3 and Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38191/abstract). Activated regions included the thalamus, the insula/frontal operculum, the secondary somatosensory cortex, the dorsolateral prefrontal cortex, the basal ganglia, and the cerebellum. Medial and lateral visual cortices were also activated. Deactivations were observed in the medial prefrontal cortex in both groups. No group differences were observed in the whole-brain analyses for pain-induced brain activity.

The visual cue for relief anticipation (Figure 4

Table 1. Demographic and clinical data on the study subjects*

Variable	Controls (n = 14)	FM patients (n = 31)
Age, years	44.2 ± 14.3	44.0 ± 11.9
Sex, % female	71.4	87.1
Symptom duration, years	–	12.5 ± 12.2
Clinical pain, 0–100 scale		
Intensity	–	34.3 ± 25.19
Unpleasantness	–	32.3 ± 26.7
Fatigue, 0–100 scale	13.0 ± 16.4	64.6 ± 22.3†
BDI, 0–63 scale	2.8 ± 3.8	17.0 ± 13.6†
WPI, no. of pain sites of a possible 19	0.4 ± 0.8	11.6 ± 8.1†
SF-36, 0–100 scale		
General health	88.6 ± 13.8	39.0 ± 23.7†
Physical function	90.4 ± 26.4	47.4 ± 26.0†
BPI, 0–10 scale		
Pain interference	0.0 ± 0.0	5.5 ± 2.0†
Pain severity	0.3 ± 0.6	5.3 ± 2.0†

* Except where indicated otherwise, values are the mean ± SD. FM = fibromyalgia; BDI = Beck Depression Inventory; WPI = Widespread Pain Index; SF-36 = Short Form 36 health survey; BPI = Brief Pain Inventory.
† $P < 0.001$ versus controls.

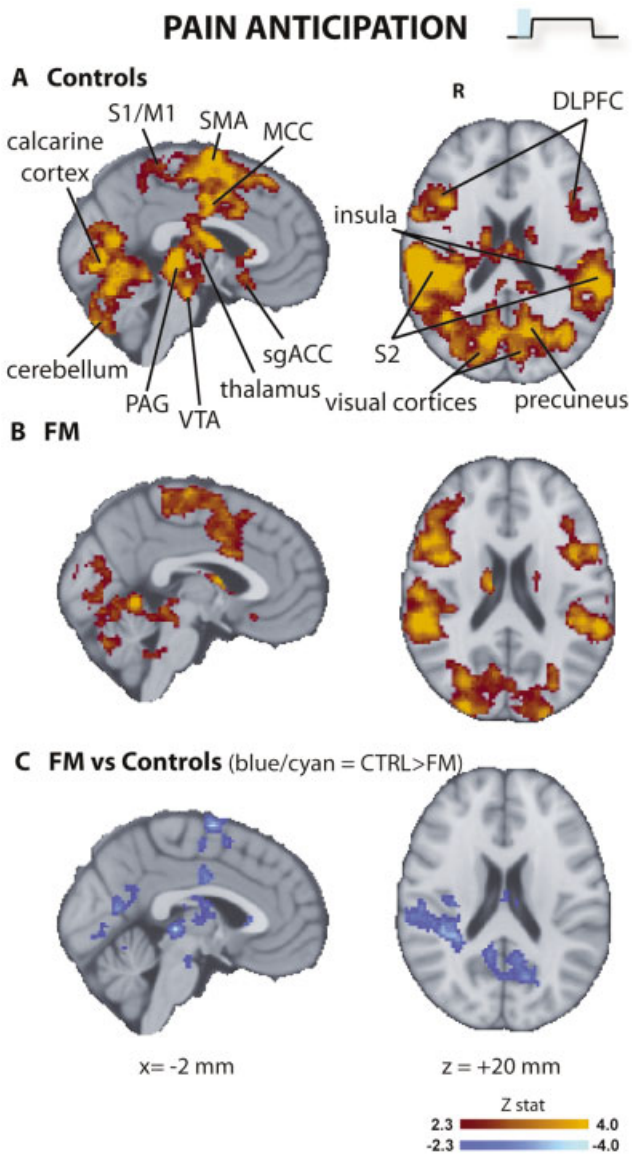

Figure 2. Responses in the brain to pain anticipation (whole-brain analyses). Responses were measured in controls (**A**) and fibromyalgia (FM) patients (**B**), and activation was measured in FM patients versus controls (**C**). FM patients exhibited lower activity in the brain in several regions. S1/M1 = primary somatosensory/motor cortices; SMA = supplementary motor area; MCC = middle cingulate area; sgACC = subgenual anterior cingulate cortex; VTA = ventral tegmental area; PAG = periaqueductal gray; DLPFC = dorsolateral prefrontal cortex. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.38191/abstract.

and Supplementary Table 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38191/abstract) produced significant activations in the primary somatosensory and motor cortices, the lateral and medial prefrontal cortices, the operculo-insular cortex, the precuneus, and visual areas in both groups. In controls, stronger BOLD responses were observed in the left primary somatosensory and motor cortices (sensorimotor representation of the leg), superior parietal lobule, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, and operculo-insular cortices compared to patients. In the whole-brain analyses, FM patients did not exhibit a stronger BOLD response to the expectancy of pain relief cue in any region compared to controls.

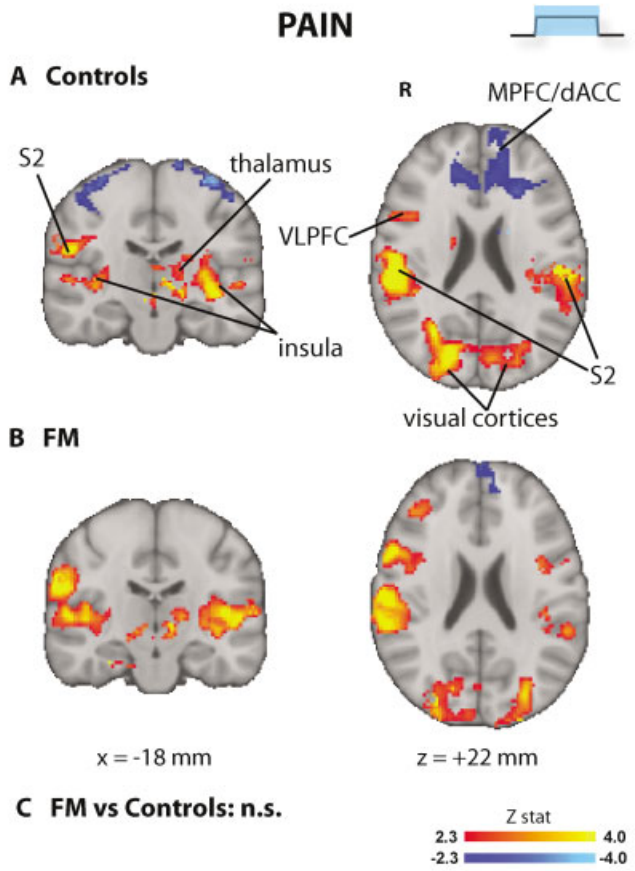

Figure 3. Responses in the brain to pain (whole-brain analyses). Responses were measured in controls (**A**) and fibromyalgia (FM) patients (**B**), and activation was measured in FM patients versus controls (**C**). In whole-brain searches, there was no statistically significant difference (NS) in the response to cuff pain between the 2 groups. S2 = secondary somatosensory cortex; VLPFC = ventrolateral prefrontal cortex; MPFC = medial prefrontal cortex; dACC = dorsal anterior cingulate cortex. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.38191/abstract.

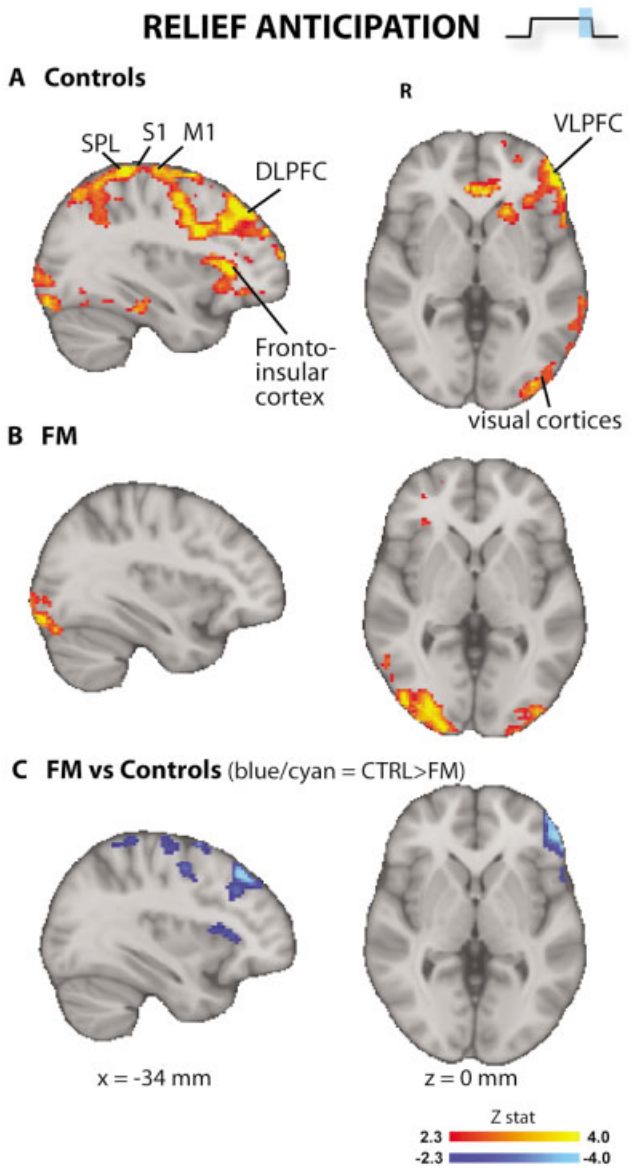

Figure 4. Responses in the brain to anticipation of pain relief (whole-brain analyses). Responses were measured in controls (**A**) and fibromyalgia (FM) patients (**B**), and activation was measured in FM patients versus controls (**C**). FM patients exhibited lower brain responses in several regions of the brain. SPL = superior parietal lobule; S1/M1 = primary somatosensory/motor cortices; DLPFC = dorsolateral prefrontal cortex; VLPFC = ventrolateral prefrontal cortex.

Imaging results—ventral tegmental area and nucleus accumbens analyses. No group differences reached statistical significance for the nucleus accumbens in the direct searches. In the right ventral tegmental area, a voxelwise direct search revealed group differences in all 3 statistical comparisons (Figure 5). Healthy controls exhibited an increase in BOLD signal during pain anticipation and pain stimulation, but a decrease during relief anticipation. In FM patients, however, these responses were either significantly reduced (pain), or null (pain anticipation and relief anticipation) (Figure 5B).

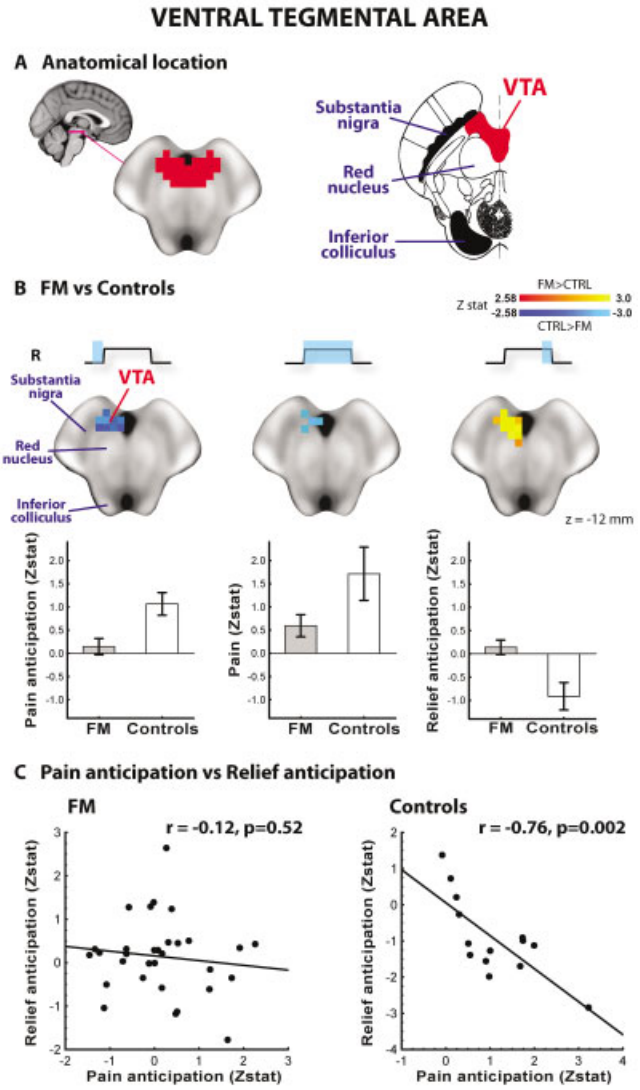

Figure 5. Direct searches in the ventral tegmental area (VTA). **A,** For the analysis of regions of interest, the ventral tegmental area mask (left) was drawn in the midbrain, medial to the substantia nigra and ventral to the red nucleus (right). Adapted, with permission, from ref. 24. **B,** There was a statistically significant reduction in responses (activations or deactivations) to anticipation of pain, pain, and anticipation of pain relief in the ventral tegmental area of fibromyalgia (FM) patients compared to controls. Bars show the mean ± SEM. **C,** Responses to pain anticipation were negatively correlated with responses to relief anticipation in the ventral tegmental area in controls, but not in FM patients.

Similar results were observed in ROI analyses that averaged the values from all voxels in the right ventral tegmental area mask. Compared to FM patients, control subjects exhibited stronger activations during pain anticipation ($P < 0.01$) and a trend toward stronger activations during pain stimulus ($P = 0.059$), while stronger deactivations were found during relief anticipation ($P < 0.05$). Using the left ventral tegmental area as an ROI, no statistically significant group differences were observed during pain stimulation or during anticipation of relief, similar to the findings of the direct search ($P > 0.6$). However, the left ventral tegmental area did reveal a statistically significant difference in the BOLD signal between FM patients and controls in regard to pain anticipation (i.e., control subjects had a stronger BOLD signal) ($P < 0.05$). In the ventral tegmental area subregion showing statistically significant group differences in all comparisons, responses to pain anticipation were positively correlated with responses to pain in both groups (control subjects [$r = 0.54$, $P = 0.048$], FM patients [$r = 0.55$, $P = 0.001$]). Responses in the ventral tegmental area to pain anticipation were also negatively correlated with responses in the ventral tegmental area to relief anticipation in the control subjects ($r = 0.76$, $P = 0.002$), but not in the FM patients ($r = -0.12$, $P = 0.52$) (Figure 5C).

DISCUSSION

Our evidence indicates differences between FM patients and controls in brain processing during pain, as well as during anticipation of pain and of pain relief. During pain anticipation (Figure 2), multiple regions were activated in healthy controls, (including the anterior cingulate cortex, the periaqueductal gray, the thalamus, the premotor cortex, and the ventral tegmental area, i.e., areas previously reported as being associated with expectancy of pain [25]), as well as other regions thought to be involved in sensory, affective, cognitive, and pain-modulatory processes (such as the primary somatosensory and motor cortices, the secondary somatosensory cortex, the dorsolateral prefrontal cortex, the fronto-insular cortex, and the basal ganglia) (26). Interestingly, brain responses to pain anticipation were significantly reduced in FM patients.

Cuff pain stimuli (Figure 3) evoked brain activity changes in regions frequently observed to be activated (the thalamus, the insula/frontal operculum, the secondary somatosensory cortex, the dorsolateral prefrontal cortex, the basal ganglia, and the cerebellum) or deactivated (medial prefrontal cortex) during experimental pain (21,26). These brain activity changes were statistically indistinguishable between groups in whole-brain analyses. Of note, we were able to observe these brain responses even if the stimuli were delivered for a longer duration (i.e., 46–74 seconds) than that used in most published fMRI pain studies. Still, the lack of activation within the primary somatosensory cortex (which contrasts with the presence of primary somotosensory cortex activations that we have previously observed with cuff pain stimuli of shorter duration [21]) could be due to the length of stimulation.

During the relief anticipation period (Figure 4), visual areas were similarly activated in both groups (likely in response to the processing of the visual cue). However, FM patients exhibited lower brain activations compared to controls in multiple regions, including the primary somatosensory and motor cortices, superior parietal lobule, ventro- and dorsolateral prefrontal and fronto-insular cortices. Overall, these results add to the growing body of literature supporting the notion that FM patients demonstrate reduced responsiveness to a variety of experimental manipulations (4,27,28).

Analyses (direct search and ROI) that were focused on mesolimbic regions revealed group differences in responses to pain anticipation, pain, and relief anticipation in the right ventral tegmental area (Figure 5). The ventral tegmental area is a dopamine-rich region that occupies the ventromedial portion of the midbrain. While dopaminergic neurons in the ventral tegmental area and other regions have been traditionally linked to processing of signals for reward, it has become increasingly clear that a portion of these cells also encode aversive/punishment signals (29). Indeed, in our healthy controls the responses in the ventral tegmental area to all 3 experimental periods were compatible with the encoding of signals of punishment and reward: activation during pain anticipation and pain stimulus, but deactivation during relief anticipation. Furthermore, responses in the ventral tegmental area during pain anticipation were positively correlated with responses during pain stimulation, and negatively correlated with responses during relief anticipation (i.e., subjects with greater activation in the ventral tegmental area during pain anticipation had greater deactivation in the same area during relief anticipation). In FM patients, however, responses in the ventral tegmental area to all experimental periods were dramatically reduced or abolished, and the activity during pain anticipation and relief anticipation was not related.

Our observation that a region rich in dopaminergic neurons, such as the ventral tegmental area, exhibits

less reactivity to all experimental periods is compatible with the results of other studies showing altered dopaminergic neurotransmission in FM patients. For instance, recent PET studies have demonstrated that FM patients exhibit reduced activity levels of DOPA decarboxylase, an enzyme involved in dopamine metabolism, in several regions including the ventral tegmental area (17). They also exhibit reduced dopaminergic brain responses to evoked pain (4) compared to healthy controls. Of note, PET studies in humans have revealed that higher binding potential of D2/D3 ligands, potentially indicative of lower levels of endogenous dopamine release, is associated with higher pain sensitivity in healthy adults as well as FM patients (4,30). Thus, altered dopaminergic neurotransmission may, at least in part, be an underlying factor for the noted hyperalgesia in FM patients (31–33), as was also observed in the present study (Figure 1).

Interestingly, lower responsiveness of the ventral tegmental area and other "reward regions" to noxious stimuli predicts lower opioid-induced analgesia in healthy subjects (34). Thus, altered responses in the ventral tegmental area to pain (as well as to pain anticipation/relief anticipation) in FM might be reflective of neural mechanisms associated with the lack of therapeutic efficacy of opioids in treating pain related to FM (opioid use for management of pain in FM is not recommended by any current guidelines [35–37]). Furthermore, recent evidence suggests a strong link between corticostriatal circuitry and chronic pain (38). This circuitry is under the modulatory control of dopaminergic midbrain nuclei including the ventral tegmental area, and therefore our study provides further support for the notion that dopaminergic neurotrasmission plays a role in the pathology underlying pain disorders.

While up to 65% of neurons in the ventral tegmental area are dopaminergic, a large portion of the remaining neurons are γ-aminobutyric acid–releasing (GABAergic) neurons (39). Recent studies have shown that most ventral tegmental area GABAergic neurons are excited by aversive stimuli, including noxious stimuli, suggesting that these cells play a role in processing signals for punishment (15,40). Notably, in the study by Cohen et al (15), these neurons exhibited a small increase in firing rate during the exposure to a conditional cue immediately preceding an aversive stimulus, and a larger increase in firing rate during receipt of the aversive stimulus itself. This activity profile was very similar to the responses we observed in the ventral tegmental area in our controls. Since GABA levels are diminished in some brain regions in FM patients (41), it is possible that reduced GABAergic neurotransmission also contributes to the group differences we observed in brain activity. However, as no direct measure of GABA or dopamine was obtained in this study, the neurochemical correlates of our results are only speculative and will need to be directly investigated.

One possible explanation for the between-group differences in activity observed in other brain regions during the pain anticipation/relief anticipation periods involves the concept of salience (i.e., the ability of a given stimulus to stand out from its background). As most patients reported experiencing some amount of ongoing pain (i.e., their clinical pain) even in the absence of cuff stimulation, the cues may have only signaled the transition from a lower level of pain to a higher level of pain (or vice versa), rather than the transition from a pain-free state to a moderately strong pain state (or vice versa), as was the case in the healthy controls. It is therefore possible that the observed differences between the groups might partly reflect a lower salience attributed by the patients to the impending onset or offset of cuff pain stimulation. Since several of the regions that were observed to be activated during the pain anticipation/relief anticipation periods (including the somatosensory, insular, cingulate, frontal, and parietal areas) have been implicated in the detection of salient changes in the sensory environment (42–44), our data at least in part support this interpretation. Moreover, stimuli with high emotional salience induce stronger activations of visual areas compared to less salient stimuli (45). Therefore, the differences between the groups with regard to visual cortex activation during pain anticipation corroborate the notion of potential differences in processing of salient events.

Furthermore, reduced brain responses to the anticipation of pain relief were observed in regions that are often implicated in placebo analgesia, including the ventrolateral prefrontal cortex, dorsolateral prefrontal cortex, and insula (46–48). Therefore, such results could be partly explained by the expectation, in FM patients, of a lower degree of pain relief, since, in their case, the end of stimulus does not mean the end of pain perception (i.e., their clinical pain continues).

Other factors might also contribute to the brain activity differences we observed between groups, such as the reduced ability of patients with FM to engage pain-coping mechanisms. Among the regions that were activated to a lesser degree during pain anticipation in FM patients was the periaqueductal gray. The periaqueductal gray is a midbrain structure that has been implicated in descending pain modulation by a large number

of studies. For instance, electrical stimulation of subregions of the periaqueductal gray in animals has been shown to reduce behavioral responses to noxious stimulation by inhibiting nociceptive dorsal horn neurons indirectly through projections to the rostral ventromedial medulla (49). Therefore, activation of the periaqueductal gray during expectancy of pain in healthy controls may reflect the engagement of the descending pain inhibitory mechanisms preparatory to the upcoming pain stimulus. According to this view, the reduced periaqueductal gray activation in FM patients would be indicative of a reduced ability to engage such coping mechanisms, a notion also supported by the results of other studies (6).

Yet another mechanism potentially contributing to reduced responsiveness in FM patients to the experimental conditions may be related to perceived helplessness. A recent study of a different chronic pain population (temporomandibular disorder) has demonstrated that there is a relationship between reported helplessness and cortical thickness in the supplementary motor area and midcingulate cortex (50). As these regions were among those exhibiting lower responsiveness to pain anticipation in FM patients in our study, future studies should investigate whether catastrophizing-related factors such as helplessness and structural brain changes may contribute to the explanation of our observations.

Several caveats should be taken into consideration. First, we did not collect behavioral data that directly measured perceived reward or punishment. Thus, linking altered responses in the ventral tegmental area in FM patients to alterations in the processing of punishment and reward is only based on the well-accepted role of this brain region in the processing of aversive/rewarding stimuli, as well as on the assumption that anticipating or perceiving a painful stimulus is a punishing experience, while anticipating relief from pain is a rewarding experience. Similarly, we did not collect behavioral data allowing us to test the hypothesis that experimental pain stimuli may be less salient for patients because of the competing ongoing clinical pain. It is also important to note that since FM patients were more sensitive to pain stimuli, they required less pressure to achieve the target pain sensation compared to the healthy controls. Thus, we cannot exclude the idea that the differences in the physical intensity of the stimulation might explain at least part of the brain effects observed in this study.

In summary, we demonstrated the existence in FM patients of pain-related alterations within brain circuitry associated with the processing of reward/punishment and salience. Our results further support the notion of a reduced ability to engage the descending pain modulatory system in these patients. While we did not directly investigate neurotransmitter release, our observations are also compatible with results of previous studies demonstrating altered dopaminergic/GABAergic neurotransmission in FM patients. These findings could contribute to our understanding of some hallmarks of FM, including augmented central processing of pain and the lack of therapeutic efficacy of opioid treatments.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Loggia had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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