Towards a neurophysiological signature for fibromyalgia

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Abstract

Patients with fibromyalgia (FM) show characteristically enhanced unpleasantness to painful and nonpainful sensations accompanied by altered neural responses. The diagnostic potential of such neural alterations, including their sensitivity and specificity to FM (vs healthy controls) is unknown. We identify a brain signature that characterizes FM central pathophysiology at the neural systems level. We included 37 patients with FM and 35 matched healthy controls, and analyzed functional magnetic resonance imaging responses to (1) painful pressure and (2) nonpainful multisensory (visual–auditory–tactile) stimulation. We used machine-learning techniques to identify a brain-based FM signature. When exposed to the same painful stimuli, patients with FM showed greater neurologic pain signature (NPS; Wager et al., 2013. An fMRI-based neurologic signature of physical pain. N Engl J Med 2013;368:1388–97) responses. In addition, a new pain-related classifier ("FM-pain") revealed augmented responses in sensory integration (insula/operculum) and self-referential (eg, medial prefrontal) regions in FM and reduced responses in the lateral frontal cortex. A "multisensory" classifier trained on nonpainful sensory stimulation revealed augmented responses in the insula/operculum, posterior cingulate, and medial prefrontal regions and reduced responses in the primary/secondary sensory cortices, basal ganglia, and cerebellum. Combined activity in the NPS, FM pain, and multisensory patterns classified patients vs controls with 92% sensitivity and 94% specificity in out-of-sample individuals. Enhanced NPS responses partly mediated mechanical hypersensitivity and correlated with depression and disability ($P_{uncorrected} < 0.05$); FM-pain and multisensory responses correlated with clinical pain ($P_{uncorrected} < 0.05$). The study provides initial characterization of individual patients with FM based on pathophysiological, symptom-related brain features. If replicated, these brain features may constitute objective neural targets for therapeutic interventions. The results establish a framework for assessing therapeutic mechanisms and predicting treatment response at the individual level.

Keywords: Fibromyalgia, fMRI, Brain, Chronic pain, Multisensory, Pressure, Machine learning, Predict

1. Introduction

Fibromyalgia (FM) is characterized by the presence of widespread musculoskeletal pain and tenderness accompanied by fatigue, cognitive/emotional, and sleep-related symptoms, occurring without any other medical explanation.[77] Besides its high prevalence and clinical relevance,[79] there is an inherent problem associated with the diagnosis of FM, in that there is an absence of laboratory findings or well-characterized pathology that is sensitive and specific for the disorder. The existence of FM as a clinical diagnosis has been therefore historically questioned.[79] The past 2 decades of research, however, have provided consistent evidence to suggest abnormal nervous system findings in patients with FM.[14] Of note, neuroimaging studies have shown augmented responses to a variety of painful stimuli in FM,[15,25,56] and altered brain structure, metabolic activity, and resting state functional connectivity in regions that are consistently involved in processing pain.[23,28,34,36,38,44,50,57,58,60,61]

In addition to pain-related changes, patients with FM show reduced tolerance (augmented unpleasantness) to nonpainful sensory stimulation (visual, auditory, olfactory, and tactile), along with abnormal brain processing of nonpainful sensory stimuli.[11,21,30,42,74] Our group[42,58] and others[31,46,53] have reported evidence suggesting that the brain systems involved in the primary cortical processing of nonpainful sensory signals and their integration may play an important role in FM pain. These studies suggest that pain in FM may be associated with (1) hyperexcitability of the nociceptive system, ie, increased transmission,[52,64,69] central amplification,[15,25,56] and/or reduced inhibitory control mechanisms[35,37] and (2) reduced opponent nonnociceptive sensory processing.[31,42,46,53,58] Despite these brain and behavioral findings, there remains a critical gap between characterizing abnormalities in FM at a group level and identifying neurophysiological markers diagnostic of FM at an individual patient level.

Here, we use a multisensory approach to identify a brain signature sensitive to FM status (vs healthy) at the individual-person level. Notably, we do not imply that the signature should differentiate FM from other chronic pain conditions with a sensitization component. We include tests of both mechanical pain and nonpainful sensory brain responses to (1) characterize the sensory processing alterations that are distinctive of FM at the central level and (2) address how such characteristic pathophysiological features relate to patients' core symptoms. As a first approach to assess alterations in central pain processing, we applied the neurologic pain signature (NPS), a multivariate brain activation pattern that was previously validated to be sensitive and specific to predict experimental pain perception at the individual-person level.[70] The NPS accurately predicts experimental pain perception but does not respond to other unpleasant, highly arousing emotional experiences.[70] Augmented expression of the NPS in FM would indicate enhanced pain-specific cerebral processing in patients. In addition, we applied cross-validated machine learning algorithms to differentiate patients with FM from healthy participants based on their brain responses to (1) pressure pain and (2) combined nonpainful visual, auditory, and tactile motor stimulation. Finally, we combined pain and multisensory brain measures to obtain a cross-validated signature for FM status.

2. Materials and methods

2.1. Ethics statement

This study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the Ethics and Institutional Review Board of the Autonomous University of Barcelona (reference number SAF2010-19434). All patients and healthy participants provided written informed consent to participate in the study.

2.2. Subjects

Seventy-two subjects participated, including 37 female patients with FM (1990 American College of Rheumatology criteria for FM)[78] and 35 female matched healthy controls (**Table 1**). Patients and healthy subjects were matched for age, education status, and handedness (all right handed, **Table 1**). The patients were consecutively recruited during clinical follow-up in the rheumatology service (CIMA, Barcelona) to provide a homogeneous sample with severe and persistent FM symptoms. Vision and hearing were normal upon neurological examination for all patients and healthy participants.

We administered the following scales in a visit before the magnetic resonance imaging (MRI) appointment: Fibromyalgia

Table 1

Demographics, illness severity, and medication regime.

	Patients with FM (N = 37)*	Healthy participants (N = 35)*	Statistics
Age (mean ± SD)	46.27 ± 7.72	43.86 ± 6.05	$t = 1.47$, $P = 0.15$
Education (y)	14.19 ± 4.47	15.09 ± 4.90	$t = 0.81$, $P = 0.42$
Illness duration (mo)	80.41 ± 52.05		
Tender points (number)	15.92 ± 1.96		
FIQ (total score)	66.86 ± 15.79		
FIQ (functional capacity)	4.81 ± 1.84		
SF-36 (perception of health)	30.33 ± 17.63		
HADS (depression)	8.89 ± 4.72		
HADS (anxiety)	11.54 ± 4.15		
Clinical pain (0-100 NRS)	72.03 ± 14.82		
			Number of patients with FM (N = 37)
Antidepressants†			
SSRI			15
NS-SSRI			3
SNRI			6
NaSSAs			1
TCA and SSRI			3
Anxiolytics			
Benzodiazepines			18
Hypnotics			
Benzodiazepinics, long half-life			1
Benzodiazepinics, medium half-life			1
Benzodiazepinics, short half-life			3
Gabapentin			10
Analgesic drugs‡			33 occasionally (11 stably)
Non-opiod (ibuprofen and paracetamol)			11
Opiod (tramadol)			6

* All subjects were right handed.
† The total number of patients receiving antidepressant medication was 28.
‡ Analgesic drugs include ibuprofen, paracetamol, and tramadol. Patients were asked to refrain from taking nonstable (rescue) nonsteroidal anti-inflammatory drug/analgesic drugs (ie, ibuprofen, paracetamol, and tramadol) 72 hours before magnetic resonance imaging assessment. The number in parenthesis corresponds to subjects taking the analgesic medications under a stable regime.
FIQ, Fibromyalgia Impact Questionnaire; FM, fibromyalgia; HADS, Hospital Anxiety and Depression Scale; NaSSAs, noradrenergic and specific serotonergic antidepressants; NRS, numerical rating scale; NS-SSRI, non-selective serotonin reuptake inhibitor; SF-36, 36-Item Short-Form Health Survey; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Impact Questionnaire (FIQ); the 36-Item Short-Form Health Survey, General Perception of Health; the Hospital Anxiety and Depression Scale (HADS).

Patients were allowed to continue with their stable medical treatment, as listed in **Table 1**, but were asked to refrain from taking occasional rescue analgesic drugs (ie, nonsteroidal anti-inflammatory drugs, paracetamol, and tramadol) 72 hours before scanning session.

Control subjects with relevant medical and neurological disorders, any form of chronic or acute pain, substance abuse, or history of psychiatric illness were not considered for inclusion. Contraindication to MRI including pregnancy was a general exclusion criterion for both groups.

Clinical pain in deep tissue was assessed using a 101-point verbal scale. A score of 0 expressed no pain and a score of 100 the most intense pain imaginable, perceived in the body as a whole, or in most of its extension, rather than referring to any focal tenderness. Patients were asked to report spontaneous pain approximately 1 hour before the scanning session (**Table 1**). All healthy participants rated "0" for this measure.

2.3. Description of functional magnetic resonance imaging tasks and stimuli used

2.3.1. Multisensory task

A block-design functional MRI (fMRI) paradigm was used, with alternating 30-second periods of rest (no stimulation) and activation (concurrent visual, auditory, and tactile-motor stimulation), completing a total of 4 rest–stimulation cycles.[42] A subset of these data (from 25 controls and 35 patients) was used in a previous publication by our group.[42] The multisensory stimuli consisted of the simultaneous presentation of visual (3 Hz, equivalent to 6 color reversals per second) full-field flashing checkerboard composed of a grid of black and white alternating squares (80 ± 10 lux) and auditory stimulation (series of 15 tones of frequencies comprised in the range of 233.1-1318.5 Hz, presented at a temporal frequency of 3 Hz, with an intensity of 75 ± 5 dB) and a finger-opposition task during which subjects were instructed to touch the tip of their right thumb with the other fingers (from index to little finger).[42] In our multisensory assessment, we were interested in a more naturalistic presentation of sensory stimuli (and motor response) that are usually combined in daily life rather than in modality-specific alterations. As a first approach, this approach allowed us to maximize signal power and challenge both sensory and motor systems efficiently.

2.3.2. Low- and high- pressure (healthy participants only) stimulation tasks

Pressure stimulation tasks involved a block design fMRI paradigm consisting of 3 conditions per stimulation cycle repeated 5 times. Each cycle began with a rest condition with pseudorandom duration (range: 20-32 seconds), followed by a brief auditory stimulus (600-millisecond tone), followed by a 6-second anticipatory period, and then a 10-second pressure pain period. Each subject was asked to rate pain intensity and unpleasantness immediately after the end of the fMRI scanning sequence (run) using a numerical rating scale (NRS) ranging from 0 (not at all painful/unpleasant) to 100 (worst pain imaginable/most unpleasant imaginable). All participants completed a low-pressure pain task first, with pressure set at 4.5 kg/cm². Approximately 10 minutes later, 28 healthy participants (out of 35) completed a second, high-pressure pain task, with stimulus intensity

individualized based on the calibration session to reliably provoke severe but tolerable pain (5.90 ± 0.62 kg/cm²), comparable to the experience of patients with FM at 4.5 kg/cm².

As in previous studies,[25,41,56] pressure pain stimuli were delivered using a hydraulic device capable of transmitting controlled pressure to 1-cm² surface placed on the subjects' right thumbnail. In a calibration session, each subject was trained to report pain intensity and unpleasantness to different pressure stimuli ranging from 2 to 9 kg/cm² (or up to tolerance threshold) using the NRS described above. A stimulus of 4.5 kg/cm² was selected to reliably provoke intense pain (above 60 in the NRS but tolerable) in the patient group. This stimulus is only slightly more intense than what was used to determine tender points during clinical assessment in patients (4 kg/cm²). The 10-second 4.5 kg/cm² was able to evoke, during the calibration assessment, a mean pain intensity of 73.15 ± 19.76 points in the patient group and a 36.47 ± 20.38 points in the healthy control group (between-group effect: $t = 7.75$, $P < 0.0005$). For healthy participants, we also determined the minimum pressure intensity that was required during the calibration session to provoke severe (above 60 in the NRS) but tolerable pain (5.90 ± 0.62 kg/cm²).

2.4. Statistical analyses

2.4.1. Behavioral analyses

Two-sample t tests (for post-scan pain intensity and unpleasantness) were computed in SPSS (IBM SPSS Statistics for Macintosh, Version 20.0).

2.4.2. Magnetic resonance imaging acquisition and preprocessing

We scanned participants on a Philips Achieva 3.0 TX system (Philips Healthcare, Best, The Netherlands), with an 8-channel phased-array head coil and single-shot echo planar imaging. Each functional sequence consisted of gradient recalled acquisition in the steady state (repetition time [TR] = 2.000 milliseconds; echo time = 35 milliseconds; flip angle = 90°; dummy volumes = 4) within a field of view of 23 cm, a 96 × 69-pixel matrix, and slice thickness of 4 mm (interslice gap, 1 mm). Twenty-two slices parallel to the anteroposterior commissure provided whole-brain coverage.

Imaging data were processed using MATLAB (v2011b; The MathWorks Inc, Natick, MA) and Statistical Parametric Mapping software (SPM8; The Wellcome Department of Imaging Neuroscience, London). Preprocessing involved motion correction, spatial normalization, and smoothing using a Gaussian filter (full-width half-maximum, 8 mm). Data were normalized to the standard SPM echo planar imaging template provided by SPM8 and resliced to 2 mm isotropic resolution in Montreal Neurological Institute space. Regarding motion correction, translation and rotation estimates (x, y, z) were <2 mm or 2°, respectively, for all the participants, and no subjects were excluded because of artifacts or head displacement/rotations.

To address the potential effects of head motion on the FM-status prediction results, we computed a single motion index per subject for each fMRI task (see full description of the method in Ref. 57; see also Ref. 55). Briefly, we computed a measure for mean interframe motion due to translation (x, y, z), mIM_{tr}, and a measure for mean interframe motion due to rotation (pitch, yaw, roll), mIM_{rot}. Although mIM_{tr} is a distance, mIM_{rot} is an angle. The combined measurement was based on an average of both $= \frac{mIM_{tr} + r \times mIM_{rot}}{2}$, where r is the approximate average distance of all brain voxels to

the rotation principal axis. The multiplicative factor r is necessary to transform the angle mIM_{rot} to its corresponding distance arc. Following previous authors, we set $r = 50$ mm.[55] Specific details about the computation of mIM_{tr} and mIM_{rot} are provided in Ref. 57; Supplementary Information file (available online at http://links.lww.com/PAIN/A340). We did not observe between-group differences in motion during the multisensory paradigm ($t = -0.28$, $P = 0.78$). However, for the pressure pain task, significant differences were observed in TR-by-TR head motion between patients with FM and healthy participants (patients > controls, $t = 2.49$, $P = 0.02$) (also between healthy subjects at the high and low-pressure intensities, $t = 2.38$, $P = 0.02$), whereas no differences emerged between patients and healthy participants when pain was matched ($t = 0.27$, $P = 0.79$). Importantly, the magnitude of the between-group difference in head motion was minimal (95% confidence interval for the head motion difference between patients and healthy participants: 0.01-0.16 mm). To account for the potential influence of head motion in the prediction model of FM status (see below, logistic multiple regression), we added the single subject measures of head motion for each task (pain and multisensory, for the sake of completeness) as independent variables in the model and verified that neither contributed significant variance to explaining the FM status (multisensory task: $t = -0.84$, $P = 0.40$; pain task: $t = 0.20$, $P = 0.84$).

To test whether motion parameters (during the pain task) were sufficiently informative to correctly classify patients from healthy participants, we used support vector machines (SVMs) with 6 motion regressors per subject as the classification features and the subjects' category (patient vs healthy participant) as the outcome. The results were not significant (cross-validated accuracy: 60% ± 5.7% [SE], $P = 0.10$). We also checked and confirmed that the time course of the "nociception-positive NPS" response (see below) on a TR-by-TR basis was not correlated with motion parameter estimates, for any regressor for any subject (all P values > 0.1).

2.4.3. First-level single-subject models for functional magnetic resonance imaging data

We used a conventional general lineal model approach as implemented in SPM8 software to estimate brain responses to (1) multisensory stimulation and (2) pressure stimulation for each subject.

For the *multisensory task*, a primary task regressor was created by convolving the sensory stimulation blocks with a canonical hemodynamic response function. The "off" (rest) condition served as an implicit task baseline. Parameter estimates were calculated at each voxel using the general linear model. A high-pass filter was used to remove low-frequency signal fluctuations (1/128 Hz). (Multisensory stimulation − baseline) contrast images for each participant were calculated.

For the *pressure stimulation task*, signal response was modeled using separate regressors for the anticipatory and the pain periods, with a hemodynamic delay of 4 seconds. In 3 previous studies using similar procedures,[22,41,56] we systematically observed that the duration of brain responses to 10-second pressure stimuli of similar intensities extends to 16 seconds (average response duration across pain processing regions),[41] which is consistent with observations by different research groups.[13,47,70] To account for this, pain-related activation was modeled using a pain condition of 16-second duration. A high-pass filter was used to remove low-frequency signal fluctuations (1/128 Hz). In agreement with our previous work,[42,56,58,70] we did not model autocorrelations. Modeling

autocorrelations has the potential disadvantage of producing biased parameter estimates when the autoregressive (AR) model assumptions are violated, which can result in reduced efficiency.[20,80] Of note, models that do not consider autocorrelation have shown to generate unbiased parameter estimates (beta values, which we use here for classification purposes), even if the data are autocorrelated[51,80] (see also Supplementary Figure 1, available online at http://links.lww.com/PAIN/A340). (Pressure stimulation − baseline) contrast images for each participant were calculated.

We studied brain response alterations during pain processing in patients with FM using 2 complementary approaches: (1) As a first test of pain-related brain responses, we applied the NPS brain signature,[70] a multivariate fMRI-based brain pattern that was validated to specifically predict experimental pain (and not other unpleasant/arousing emotional experiences) in humans. The goal of this approach was to use a defined marker or process that has been well characterized in healthy individuals to test for abnormalities in the patient population. An advantage is that the NPS was trained to track pain intensity in a fine-grained way across multiple levels of stimulus intensity and was tested for specificity to pain and generalizability across a number of independent studies. (2) Because the NPS may not be sufficient to capture all pain-related differences between patients and controls, a second approach was to train a classifier optimized to discriminate patients with FM from controls. This pattern identifies pain-related signals that may be missed by the NPS. This second approach was also applied to the multisensory task (see below).

2.4.4. Computing Neurologic Pain Signature responses

We computed for each subject (patient with FM or healthy participant) a single scalar value representing their expression of the NPS pattern in response to pressure pain (using the contrast [pressure stimulation − baseline] images, as detailed below).

For this analysis, we separated NPS regions likely to be related to nociceptive pain (associated with pain-evoked activation in the NPS) from those that play other modulatory roles (associated with pain-evoked deactivation in the NPS). In most of the regions in the NPS, pain is associated with increased overall activity. Such regions include the major targets of ascending nociceptive afferents, including the thalamus, primary and secondary somatosensory regions (SI/SII), posterior, mid and anterior insula and adjacent opercula, midbrain, dorsal anterior cingulate cortex (ACC), inferior frontal gyrus and amygdala (Supplementary Table 1, available online at http://links.lww.com/PAIN/A340, and **Fig. 1**). We refer to pattern responses in this set of regions as the "nociception-positive NPS" (NPSp). In a subset of other medial regions, including the perigenual ACC (pgACC) and the posterior cingulate (PCC)/precuneus/paracentral lobule, pain was associated with deactivation in the original NPS pattern. These regions are not strongly linked to nociception and are not direct targets of nociceptive afferents, rather they have been associated with a variety of affective, autonomic, social, self-referential, and decision-making functions.[62] We refer to responses in this set of regions as the "nociception-negative NPS" (NPSn) and analyze this pattern separately from the NPSp due to its differential functional characteristics and considering the particular role of these regions, mostly the pgACC, in chronic pain. Of note, the local pattern of voxel weights is exactly the same as in the original NPS within the 2 NPS components (NPSp and NPSn). Supplementary Text 1 provides
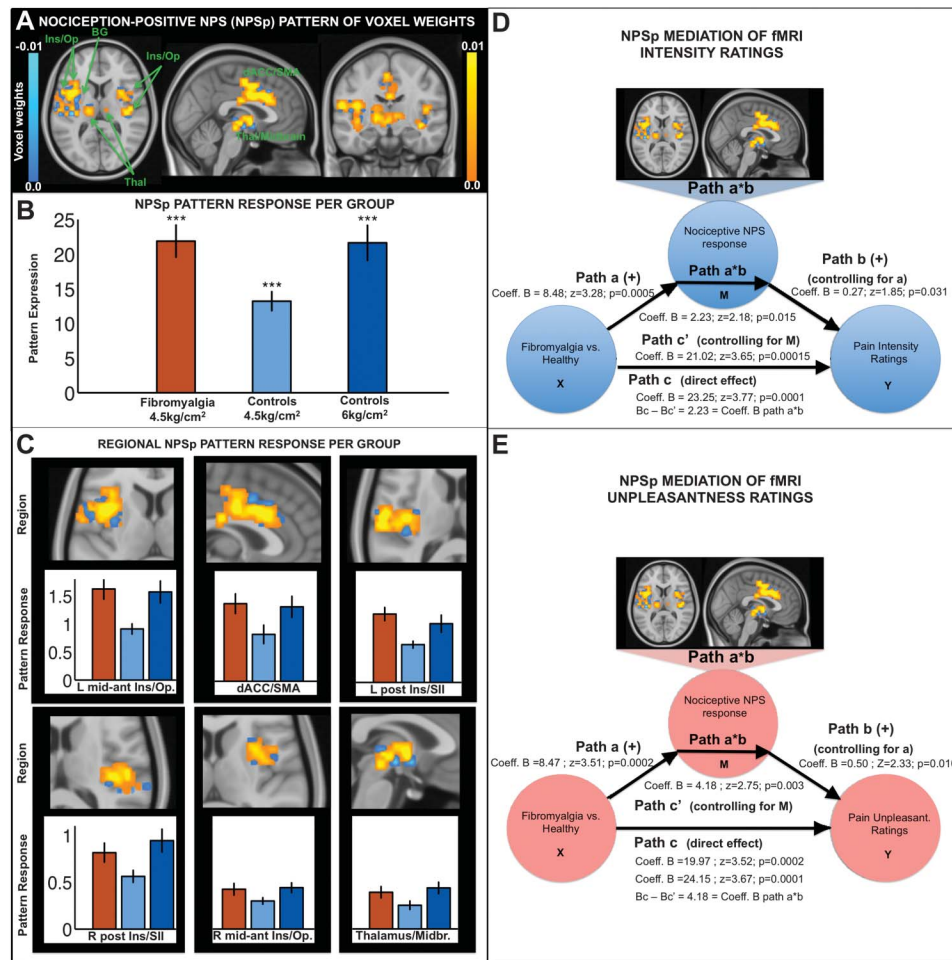
Figure 1. Nociception-positive neurologic pain signature (NPS) (NPSp) map of voxel weights (A); pattern response per group (B); and contiguous regions (C). Error bars represent standard errors of the mean. ***$P < 0.0001$. Responses to low-intensity stimulation in (B) were 21.87 ± 14.00 ($t = 9.5$, $P < 0.0001$) in patients with fibromyalgia (FM) and 13.21 ± 8.02 in healthy participants ($t = 9.74$, $P < 0.0001$). Responses to high-intensity stimulation were 21.62 ± 13.31 in healthy participants ($t = 9.74$, $P < 0.0001$). NPSp pattern response significantly mediates (partial mediation) the relationship between clinical category (FM diagnosis present vs absent) and pain intensity (D), and pain unpleasantness (E) ratings in response to 4.5 kg/cm^2 painful pressure. All coefficients in the mediation models have been tested for significance using 10,000 bootstrap tests. One-tail P-values are reported as we had directional a priori hypotheses (patients with FM will show greater NPS responses; and the greater the NPS response, the higher the pain ratings). ant, anterior; BG, basal ganglia; coeff, coefficient; dACC/SMA, dorsal anterior cingulate cortex and supplementary motor area; fMRI, functional magnetic resonance imaging; Ins, insula; L, left; Midbr, midbrain; Op, operculum; post, posterior; R, right; Thal, thalamus.

a detailed description of the rational for computing NPSp and NPSn and the procedure used to characterize them (available online at http://links.lww.com/PAIN/A340).

2.4.5. Mediation analysis

We tested 2 separate mediation models to assess whether the relationship between FM status (FM vs healthy) and pain ratings during the fMRI pain task (intensity—model 1 and unpleasantness—model 2) were significantly mediated by NPS brain responses. The mediation analysis tested several joint hypotheses: Path *a* tested whether FM status (FM vs healthy) predicts NPSp responses. Path *b* tested whether NPSp responses predict subjective ratings of intensity (or unpleasantness), controlling for FM status. Finally, the Path *a* × *b* tested the mediation effect, ie, whether NPSp responses during pressure pain explain a significant proportion of the covariation between FM status and subjective pain ratings. The analyses were conducted using the mediation toolbox (http://wagerlab.colorado.edu/tools) that has been used and described extensively in

a previous work (eg, Ref. 71) with bias-corrected, accelerated bootstrap tests.

2.4.6. Multivariate pattern-based classification of patients with fibromyalgia vs healthy controls

We performed 2 analyses using linear SVMs to discriminate patients with FM and controls based on whole-brain activation patterns. The first analysis used activation patterns during painful pressure at 4.5 kg/cm^2 pressure stimulation (FM-pain) and the second analysis used activations during non-painful multisensory stimulation (multisensory). The SVM was implemented in the Spider Toolbox (http://people.kyb.tuebingen.mpg.de/spider). It identifies a hyperplane (direction in multidimensional voxel space) that separates the 2 groups. Distances from the hyperplane are related to the likelihood a participant belongs to the patient vs control class and were used in the logistic regression analysis below.

The FM-pain classifier was based on the (pressure stimulation − baseline) contrast, and the multisensory classifier was based on the

(multisensory stimulation − baseline) contrast. In each analysis, we used leave-2-subject-out cross-validation, which ensured that the patterns we identified were always tested on new, out-of-sample individuals (see Supplementary Information, available online at http://links.lww.com/PAIN/A340). Accuracy (sensitivity and specificity) was based on the cross-validation, and the final weight map was based on the full sample and was thresholded using a bootstrap test ($q < 0.05$ false discovery rate (FDR)-corrected; for a detailed description of the SVM analysis and the bootstrap test, see Supplementary Text 2, available online at http://links.lww.com/PAIN/A340).

2.4.7. Logistic multiple regression to develop a combined classifier for fibromyalgia status

We used logistic regression to combine results from the 3 fMRI-based classifiers (NPS, FM-pain, and multisensory) into a single signature of FM status. The predictors in the regression were: (1) the NPSp response, (2) the NPSn response, (3) the cross-validated FM-pain signature response (distance from the hyperplane), and (4) the cross-validated multisensory signature response.

Logistic regression results were used to calculate sensitivity, specificity, and the area under the receiver operating characteristic curve. We assessed these values for each fMRI-based classifier (NPSp, FM-pain, and multisensory) independently and for the combined model.

2.4.8. Multivariate brain pattern responses and medication status

To examine the relationship between medication status and brain pattern responses, we performed a series of 2-sample t tests to compare between-group differences in pattern response between medicated and nonmedicated patients.

2.4.9. Multivariate brain pattern responses and clinical severity

We also tested whether the multivariate fMRI patterns used to classify FM status were correlated with clinical symptom severity. We performed linear regression (stepwise procedure in SPSS), including the 4 brain-derived (cross-validated) pattern response values as predictors (NPSp, NPSn, FM-pain, and multisensory) and each of the clinical measures as the dependent variable in 1 of 3 regression models (clinical pain, FIQ, and HADS depression scores). We included a fourth predictor representing the presence or absence of anxiolytic or antidepressant medication in each model, considering the significant correlation between NPS responses and antidepressant and anxiolytic medication status (further described in the Results section). For completeness, we also assessed zero-order Pearson correlations between brain measures and clinical symptom severity in patients with FM.

3. Results

3.1. Enhanced pressure pain sensitivity in patients with fibromyalgia

In response to the low-pressure intensity fMRI task (4.5 kg/cm^2), patients with FM (vs healthy participants) reported increased pain intensity (mean ± SD, 71.71 ± 14.47 for patients with FM, 48.48 ± 18.31 for healthy participants; between-group effect: $t = 5.95$; $P < 0.0005$) and unpleasantness (68.24 ± 18.84 for patients with FM, 44.11 ± 19.98 for healthy subjects; between-group effect: $t = 5.24$, $P < 0.0005$). In the high-pressure intensity task (~6 kg/cm^2 ± 0.62), healthy subjects reported equivalent pain levels as patients

with FM stimulated at low pressure ($t = 0.61$, $P = 0.54$ for intensity and $t = 0.54$, $P = 0.59$ for unpleasantness).

3.2. Neurologic pain signature responses in patients with fibromyalgia vs healthy controls

Figure 1A shows the NPSp pattern. Patients with FM and healthy subjects (at both stimulation intensities) showed significant NPSp responses, shown in **Figure 1B**. Responses to the low-pressure fixed intensity (4.5 kg/cm^2) were greater for patients with FM than for healthy participants ($t = 3.24$; $P = 0.002$), consistent with hypersensitivity to mechanical pain in FM. When subjective pain was matched between groups by comparing healthy participants experiencing high pressure (6 kg/cm^2 ± 0.62) to patients with FM experiencing low pressure (4.5 kg/cm^2), NPSp responses for both groups were virtually identical ($t = 0.07$, $P = 0.94$), suggesting that subjective reports of pain were proportional to pain-specific NPSp responses.

We also examined local signature responses in each contiguous region of the NPSp (**Fig. 1C** and Supplementary Table 1; available online at http://links.lww.com/PAIN/A340). Comparisons between patients with FM and healthy participants showed significantly greater NPSp responses to low-pressure intensity in patients with FM in all regions tested, with one exception (the inferior frontal gyrus). When subjective pain was matched (high pressure in healthy participants vs low pressure in patients with FM), local pattern responses were virtually identical for all regions.

Mediation analyses supported the conclusion that FM vs healthy participant difference in pain intensity and unpleasantness was significantly partly mediated by NPSp brain responses (**Figs. 1D–E**).

We also studied pattern responses in the heteromodal regions of the NPSn component, which may have pain modulatory functions but which are not considered nociceptive targets (fully described in Supplementary Figure 2, Supplementary Table 1, available online at http://links.lww.com/PAIN/A340). In the original NPS map, increased pain was associated with deactivation in these regions (negative weights, blue-colored regions in Supplementary Figure 2, available online at http://links.lww.com/PAIN/A340). However, NPSn regions in this study showed pain-evoked activation (not deactivation). Patients showed significant pain-evoked activation in both pgACC and PCC/precuneus/paracentral lobule regions of the NPSn, whereas healthy subjects showed significant pain-evoked activation only in the PCC/precuneus/paracentral lobule cluster. For simplicity, pattern response magnitudes are always signed such that increases in pattern response indicate increases in pain activation in these regions. Both patients with FM at low pressure and healthy participants at high pressure showed significant NPSn pattern response (FM: 1.56 ± 1.96 [mean ± SD]; $t = 4.82$, $P < 0.00005$; healthy participants, low pressure: 0.30 ± 1.18; $t = 1.49$, $P = 0.15$; healthy participants, high pressure: 1.04 ± 1.61; $t = 3.40$, $P = 0.0021$). Patients with FM showed significantly greater pattern response in NPSn regions than healthy controls (all receiving 4.5 kg/cm^2, $t = 3.27$, $P = 0.002$; ie, greater activation in such regions; Supplementary Figure 2, available online at http://links.lww.com/PAIN/A340). Equating pain perception between groups again eliminated the FM vs healthy participant difference ($t = 1.14$, $P = 0.258$). Additionally, in healthy participants, NPSn responses were stronger (ie, greater activation) in the high-pressure than in the low-pressure condition ($t = 2.09$, $P = 0.04$). Analyses of individual regions within the NPSn are summarized in Supplementary Figure 2 and Supplementary Table 1 (available online at http://links.lww.com/PAIN/A340). Interestingly, the pgACC showed pain-evoked activation only for patients (and not for healthy participants

at high pressure). Both NPSn regions (pgACC and PCC/precuneus) exhibited stronger response for patients than healthy participants at matched pressure. Matching pain intensity across groups resulted in statistically equivalent activation in PCC/precuneus but a trend ($P =$ 0.10, Supplementary Table 1, available online at http://links.lww.com/PAIN/A340) toward greater activation in the pgACC in patients. Furthermore, there were no between-group differences in pgACC activity between healthy participants at low and high pressure ($P =$ 0.48, Supplementary Table 1, available online at http://links.lww.com/PAIN/A340), suggesting that this region does not contribute to pain intensity encoding in healthy participants.

We finally assessed whether the NPSp response to low-pressure intensity performed significantly better than chance in classifying FM status (present vs absent) and found that it classified 68% ± 5.5 (SE) of the cases correctly ($P = 0.0029$). In addition, NPSn responses to low pressure classified FM status with 71% ± 5.3 (SE) accuracy ($P = 0.0004$), suggesting that greater pain-evoked activation in NPSn regions at low pressure is an identifying feature of FM. Note that the 2 classification accuracy values are not statistically different from each other.

3.3. A new pain-related classifier map (fibromyalgia-pain) discriminates patients with fibromyalgia from controls

The FM-pain classification brain pattern (**Fig. 2**, Supplementary Table 2; available online at http://links.lww.com/PAIN/A340) was characterized by augmented activity in patients with FM in regions associated with sensory integration (second somatosensory cortex (SII)/parietal operculum extending into mid-insula) and self-referential/"default mode" network regions (including dorso-medial prefrontal cortex [PFC; all $q < 0.05$ FDR corrected]). At a lower level of significance ($P < 0.001$), a larger extended network was observed that included augmented pain-related responses in ventromedial PFC/subgenual ACC and PCC. Reduced activity in patients with FM was found in a region considered important for pain and emotion regulation, the dorsolateral PFC ($q < 0.05$ FDR corrected). This pattern, when applied to new test participants, classified patients with FM vs controls with 70% ± 5.4% accuracy, $P = 0.0009$. Sensitivity was 74% (confidence interval [CI]: 62%-86%) and specificity was 66% (CI: 53%-79%).

3.4. A new nonpainful multisensory classifier map discriminates patients with fibromyalgia from controls

The multisensory classification pattern (**Fig. 3**, Supplementary Table 3; available online at http://links.lww.com/PAIN/A340) showed enhanced activity in patients with FM in heteromodal regions associated with multisensory integration (posterior-mid insula/operculum), self-referential/"default mode" network regions (including the PCC/precuneus and dorsomedial PFC), and an anterior lingual region proximal to the parahippocampal gyrus. Reduced activity in patients with FM was found in primary/secondary sensory areas (occipital and superior temporal regions) associated with visual and auditory processing, respectively; lateral cerebellum; basal ganglia (dorsal and ventral putamen and pallidum); diencephalon (consistent with subthalamic and hypothalamic regions); dorsolateral PFC; and midbrain. This pattern of activity, when applied prospectively to new test participants, classified patients with FM and healthy participants with a cross-validated accuracy of 89% ± 3.7% (SE), $P < 0.0000005$; sensitivity: 84% (CI: 73%-93%) and specificity: 94% (CI: 87%-100%).

To check for a more global brain functional reorganization in patients with FM, we also tested whether the FM-pain pattern described above could accurately classify patients vs controls using images from the multisensory task and vice versa. Indeed, FM-pain pattern responses computed using individual person-level multisensory contrast images accurately classified FM status (classification accuracy: 86% ± 4.1%; $P < 0.0001$ sensitivity: 95% [88%-100%], specificity: 77% [64%-88%]). Conversely, multisensory pattern responses computed using individual pressure pain contrast images also classified FM status (classification accuracy: 76% ± 5.0%; $P < 0.0001$ sensitivity: 65% [CI: 51%-78%], specificity: 89% [CI: 79%-97%]). Thus, the 2 brain classifiers may in part reflect a more general (task-nonspecific) brain reorganization in FM that is not specific to any one sensory modality.

3.5. Combined neural classifier using pain and multisensory brain measures

This analysis aimed to predict FM status by combining pattern response values for the NPSp, NPSn, FM-pain, and multisensory patterns using logistic regression. Three of the 4 pattern responses significantly contributed to the prediction of FM status while controlling for the others (NPSp_$t = 2.16$ [$P = 0.03$], FM-pain_$t = 2.03$ [$P = 0.04$], and multisensory_$t = 4.22$ [$P < 0.0005$]), whereas the NPSn was not significant ($t = 0.09$, $P = 0.924$). **Figure 4** shows the group mean in the joint space of NPSp/FM-pain and multisensory patterns. The combined classifier was able to discriminate patients from healthy participants with a cross-validated accuracy of 93% ± 3.0% (SE), $P < 0.0000005$; sensitivity: 92% (CI: 84%-98%) and specificity: 94% (CI: 87%-100%).

3.6. Associations between brain pattern responses and medication status in patients with fibromyalgia

No significant effect of analgesics (either opioid-dependent [tramadol] or non-opioid dependent [ibuprofen and paracetamol]), hypnotics, or gabapentin was found on pattern response values for any of the 4 brain patterns, ie, NPSp, NPSn, FM-pain map, and multisensory response (all $P > 0.10$). A significant association was found between anxiolytic/antidepressant medication and NPS measures. Anxiolytic medication (present in 18 out of 37 patients) was significantly associated with NPSn pattern response values ($t = 2.29$, $P = 0.03$), indicating that medicated patients showed greater pain-evoked activation in pgACC and PCC/precuneus regions than patients who were not receiving anxiolytic medication. In addition, antidepressant medication, which is currently prescribed as a standard treatment for FM and was used in 76% of patients in this sample, was associated with greater NPSp ($t = 3.74$, $P = 0.001$) and NPSn responses (ie, increased activation; $t = 2.51$, $P = 0.016$). These results indicate that patients with FM receiving stable treatment with antidepressants showed significantly greater NPS responses than untreated individuals.

We also found a significant association between antidepressant/anxiolytic medication and clinical severity. Specifically, a variable representing presence of antidepressant/anxiolytic medications (0: no antidepressant neither anxiolytic medication; 1: presence of either antidepressant or anxiolytic medication; and 2: presence of both antidepressant and anxiolytic medication) was positively correlated with HADS depression ($r = 0.325$, $P = 0.049$) and FIQ scores ($r = 0.341$, $P = 0.039$).

Importantly, after controlling for clinical severity (including clinical pain, HADS, and FIQ scores as covariates), the
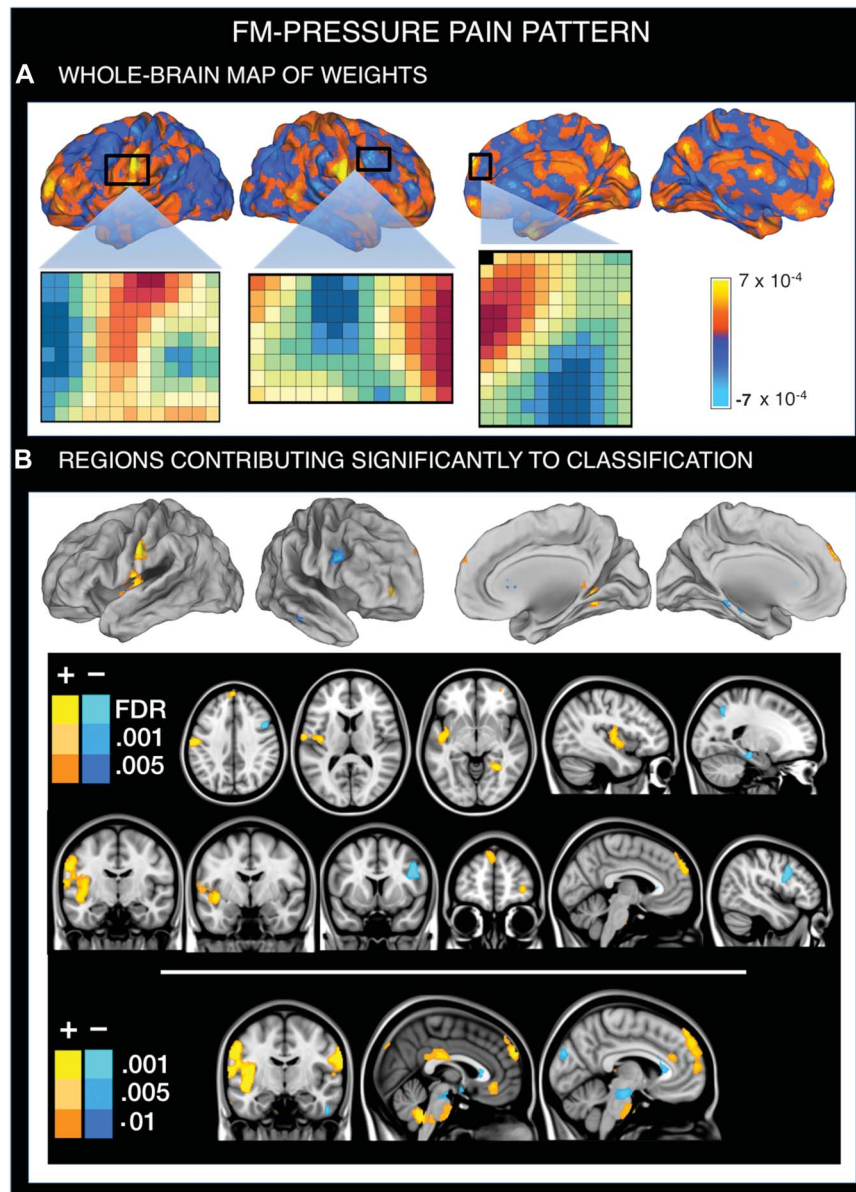
Figure 2. Multivariate brain pattern that predicts fibromyalgia (FM) status on the basis of brain activation during painful (pressure) stimulation. Positive weight values reflect higher pain-evoked activation in patients with FM relative to healthy participants, whereas negative weight values reflect reduced pain-evoked activation in patients with FM. (A) The support vector machine pattern of whole-brain voxel weights that optimizes classification of patients with FM and healthy participants. We provide the voxel-by-voxel weights for 3 representative regions (anterior SII, right dorsolateral, and dorsomedial prefrontal cortex) to illustrate the concept of weighted pattern. (B) Regions whose voxel weights contributed most reliably to the prediction of FM status ($q < 0.05$ FDR corrected for the first 2 rows; P-uncorrected <0.001 to further illustrate the findings).

relationship between anxiolytic and antidepressant use and both NPSp and NPSn responses became nonsignificant (all $P > 0.1$). These findings suggest that the observed relationship between medication use and brain measures may reflect common influences of symptom severity on both measures; that is, greater symptom severity is associated with both increased medication use and larger NPS responses.

3.7. Associations between brain pattern responses and clinical symptoms in patients with fibromyalgia

Multiple regression analyses using brain pattern responses (NPSp, NPSn, FM-pain, and multisensory) to predict symptom severity in patients with FM showed that several brain measures

correlated with FM symptoms, as illustrated in **Figure 5**. In each multiple regression model, we included a predictor representing the presence or absence of anxiolytic/antidepressant medication, to control for medication effects on symptom severity. Greater levels of clinical pain were predicted by a combination of greater FM-pain pattern responses ($t = 2.14$, $P = 0.039$) and greater multisensory pattern responses ($t = 2.88$, $P = 0.007$). The NPSp and NPSn values were not predictive, either individually or in stepwise multiple regression (all $P > 0.10$). Higher FIQ scores (assessing functional impairment associated with the disease) were predicted by a trend toward stronger NPSn responses ($t = 1.92$, $P = 0.06$), indicating that greater pain-evoked activation in NPSn regions was associated with marginally greater FIQ scores. Other measures were not predictive, either alone or in stepwise
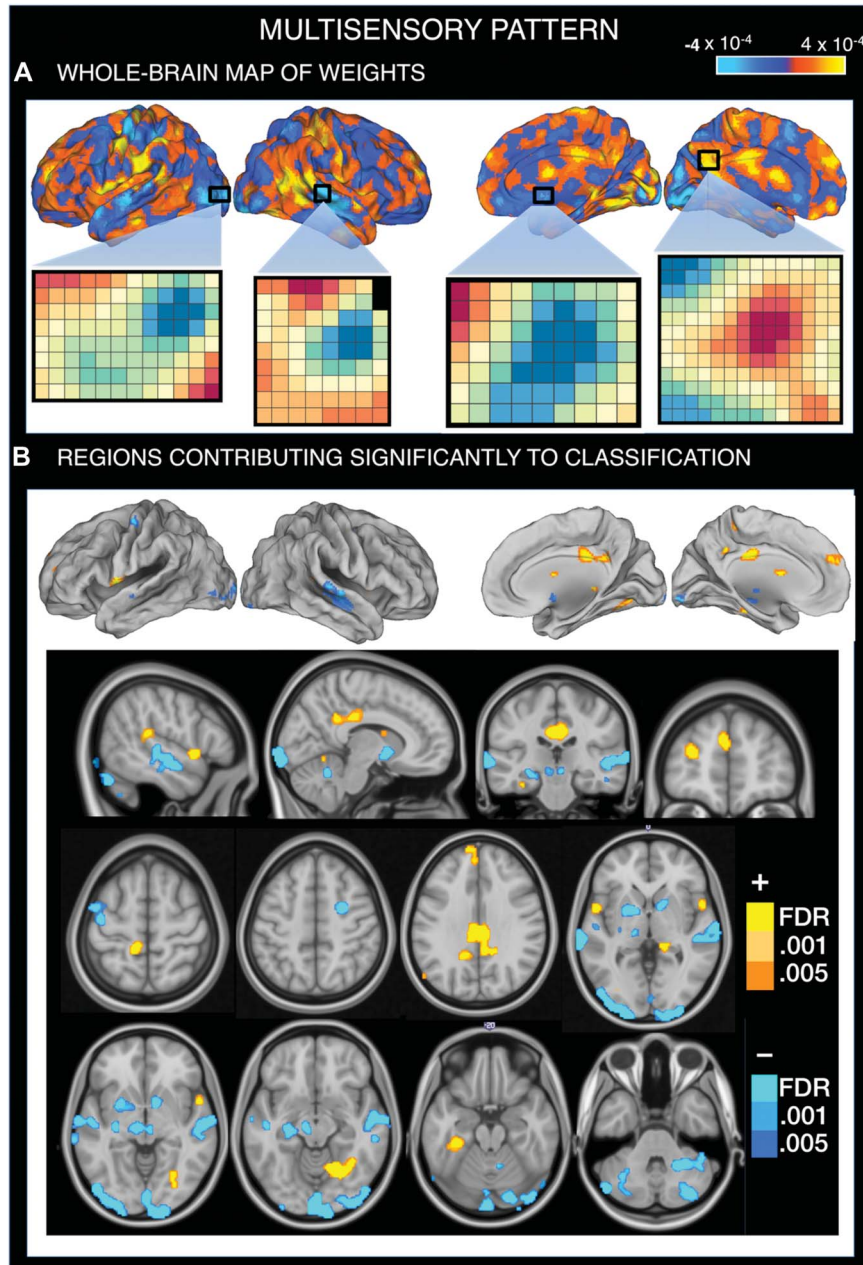
Figure 3. Multivariate brain pattern that predicts fibromyalgia (FM) status on the basis of brain activation during multisensory stimulation. Positive weight values reflect higher multisensory-evoked activation in patients with FM relative to healthy participants, whereas negative weight values reflect reduced multisensory-evoked activation in patients with FM. (A) The support vector machine pattern of whole-brain voxel weights that optimizes classification of patients with FM and healthy participants. We provide the voxel-by-voxel weights for 4 representative regions (visual cortex, auditory cortex, basal ganglia, and posterior cingulate) to illustrate the concept of weighted pattern. (B) Regions whose voxel weights contributed most reliably to the prediction of FM status (FDR corrected). The top row matches the view of (A), showing that the most reliably predicting voxels correspond to those showing the highest and lowest weights. The last 3 rows represent sagittal, coronal, and axial views showing all predictive voxel clusters.

regression (all $P > 0.10$). Greater depressive symptomatology (HADS depression) was also predicted by stronger NPSn responses ($t = 2.09$, $P = 0.04$) but not by other measures (all $P > 0.10$). Our correlation findings are preliminary and need further replication in larger samples (see Supplementary Table 4, available online at http://links.lww.com/PAIN/A340).

3.8. Brain pattern responses and time since diagnosis

There was no significant association between time since diagnosis (surrogate measure for time exposed to the disorder)

and brain pattern responses (NPS, FM-pain, and multisensory: $P > 0.1$).

4. Discussion

Diagnosing FM based on objective brain measures is important for several reasons. The status of FM as a disorder with objective physiological dysfunction has been questioned, in part because it is unclear that central[23–25,28,32–34,36,39,42,49,50,56,58] and peripheral changes[52,64,69] are sufficient to diagnose FM and explain symptoms. Objective brain-based signatures can reveal patterns
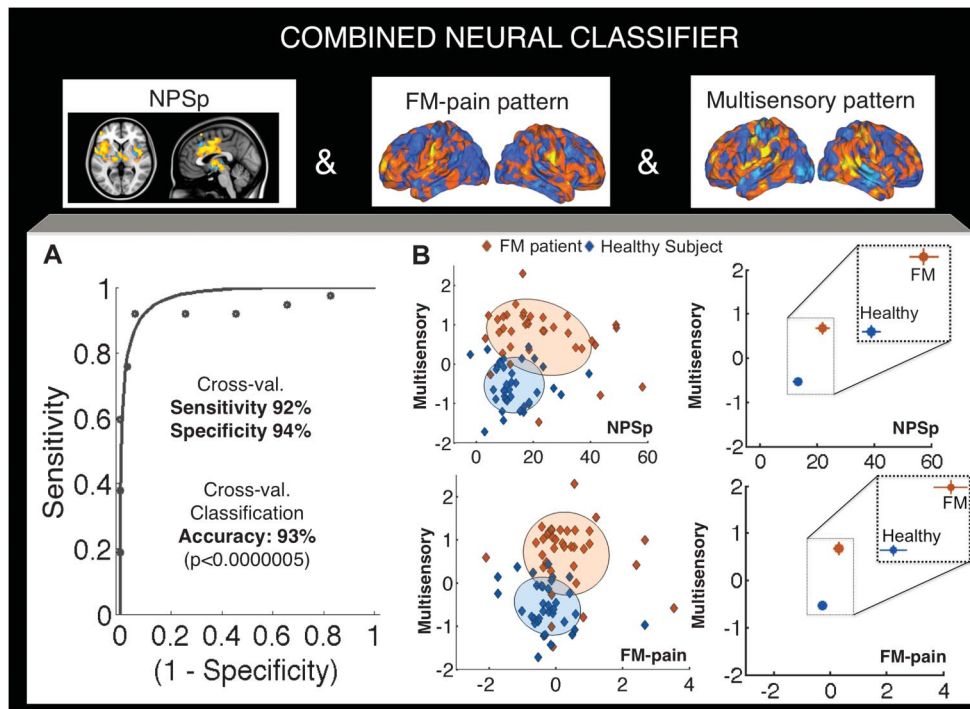
Figure 4. Sensitivity and specificity of the combined neural classifier including nociception-positive neurologic pain signature (NPSp), fibromyalgia (FM)-pain, and multisensory responses (cross-validated) for each subject. (A) The receiver-operating characteristic plot displaying sensitivity and specificity properties for the combined classifier. (B, left panels) The individual subjects' data in the join space of NPSp and multisensory or FM-pain and multisensory pattern responses. The shadowed areas represent 95% confidence regions for each group. The coefficients of correlation between pattern expression scores for healthy participants are: multisensory and NPSp, $r = 0.17$ ($P = 0.92$), multisensory and FM-pain, $r = -0.26$ ($P = 0.12$), and NPSp and FM-pain, $r = 0.015$ ($P = 0.93$). In addition, for patients with FM: multisensory and NPSp, $r = -0.24$ ($P = 0.14$), multisensory and FM-pain, $r = -0.09$ ($P = 0.59$), and NPSp and FM-pain, $r = 0.39$ ($P = 0.017$). (B, right panels) represent the group means (and SE) in the same spaces. Outlier tests were performed (≥ 3.5 SD from the mean of the subject's group). Only one control showed a value more similar to the fibromyalgia group than to the healthy control group ($z = 3.93$) for the FM-pain pattern.

of neurophysiological alterations characteristic of FM (vs healthy), potentially establishing a specific neurological component to the disorder.

Here, we identify a set of 3 brain patterns based on fMRI responses to pressure pain and nonpainful multisensory stimulation. These patterns, taken together, discriminate FM from matched healthy controls with 92% sensitivity and 94% specificity. Although we take this as a provisional "signature" for FM, we do not imply that these patterns are unique to FM or that they differentiate it from other conditions. Multifocal pain and widespread mechanical hypersensitivity are common features of multiple chronic pain conditions.[54,75] Given the overlap in symptoms and comorbidities across disorders,[54,75,76] which clinical categories are respected at the neurophysiological level and which clinical features are most likely represented in a continuum, still remain open, empirical questions. Exploratory analyses suggested that the 3 component patterns are correlated with clinical symptoms. Individual patients with FM may vary in the expression of the different brain patterns we identified, which may lead to the characterization of new FM subtypes.

These results show that fMRI may serve as a useful component of multimodal FM assessments. Previously, heart rate variability[40] and performance in specific fitness tests[3] have shown moderate-to-strong separation of patients and healthy participants. Although these measures are useful and are easy to deploy, they are not suitable for addressing the neurophysiological mechanisms of FM. Previous attempts have established neurophysiological differences in pain-related processing in patients with FM[15,24,25,56] but have not yet successfully discriminated patients from healthy participants at the individual-person level.[67] A recently published study based on

brain anatomy findings shows ability to discriminate patients with FM with from 53% to 76% accuracy in different data sets.[61] Our ability to classify with 93% accuracy in the present study relies strongly on the joint consideration of responses to nociceptive and nonpainful multisensory stimuli, following previous work.[42,56,58]

4.1. Brain features diagnostic of fibromyalgia

4.1.1. Combined pain-multisensory neural classifier

Our study provides 3 distinct neural targets for objective patient characterization. A model combining: (1) enhanced responses in the NPSp, a pain-specific brain network, (2) a pattern of brain responses to painful pressure (FM-pain pattern), and (3) a pattern of extranociceptive multisensory responses, differentiated patients with FM vs healthy participants with 93% cross-validated accuracy. The 3 effects are theoretically significant. Stronger NPSp responses mediated mechanical hyperalgesia in FM and were associated with a trend to greater depression; stronger FM-pain and multisensory responses were associated with greater clinical pain. Thus, the combined model is most likely to be useful for clinical and translational purposes, although either feature might also be used alone. Although the NPSn was not significant in the final model, NPSn responses may nonetheless be important for assessing and understanding functional aspects of FM.

4.1.2. Pain-related patterns

The *NPSp pattern* showed an augmented response in FM when the stimulus intensity was matched, but not when subjective pain
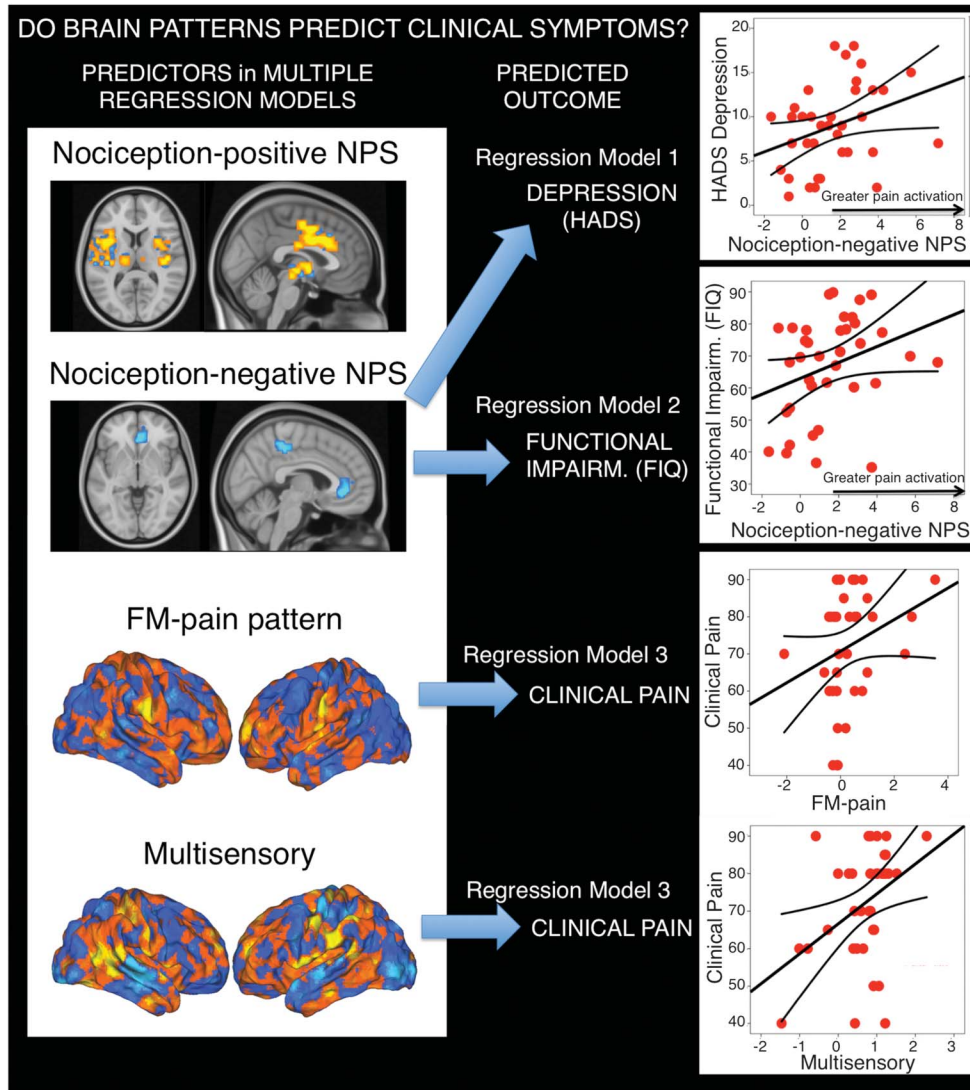
Figure 5. Prediction of symptom severity using brain patterns (nociception-positive neurologic pain signature [NPSp], nociception-negative neurologic pain signature [NPSn], fibromyalgia [FM]-pain, and multisensory) in multiple regression models. The blue arrows indicate statistically significant predictors for each multiple regression analysis model described in the main text. The straight lines in the plots are the standard linear fit lines for each regression model, and the 2 additional lines in each plot correspond to the confidence intervals for the mean. Of note, the correlation findings reported here are preliminary and need further replication in multiple samples. The right top panel illustrates the correlation between NPSn pattern responses and Hospital Anxiety and Depression Scale (HADS) depression scores in patients ($r = 0.333$, $P = 0.044$); the next panel illustrates the correlation between NPSn pattern responses and functional impairment scores ($r = 0.309$, $P = 0.063$, 2-tailed); lastly, FM-pain and multisensory responses jointly and significantly contributed to the prediction of clinical pain (main text). Here we present the raw correlations between clinical pain and FM-pain pattern responses ($r = 0.279$, $P = 0.094$) and clinical pain and multisensory pattern responses ($r = 0.393$, $P = 0.015$). To minimize the influence of potential extreme values while retaining the full sample (which is important for evaluating person-level "signatures"), we also conducted Spearman rank-correlation tests, which revealed the same pattern of results. FIQ, Fibromyalgia Impact Questionnaire.

was matched. It was a significant mediator of mechanical hypersensitivity in patients. Thus, NPSp responses are enhanced in patients in proportion to their augmented subjective experience of pressure-induced pain and are consistent with previous evidence supporting peripheral (Refs. 52,64,69) and central (Refs. 10,45,58,66) sensitization in FM. The current study cannot determine whether this enhancement reflects a change in the gain of the NPSp per unit stimulus intensity or simply reflects enhanced afferent input. Future studies could begin to disentangle these alternatives by testing multiple stimulus intensities in both patients and controls.

Rather than being limited to regions associated most strongly with emotional or evaluative aspects of pain (eg, anterior insula, ACC, lateral PFC), our findings showed a distributed enhancement

of nociceptive processing affecting all major NPSp regions. In agreement with previous observations[25,56] and considering the validation properties of the NPS, the results provide evidence of augmented pain-specific responses in FM, consistent with peripheral/central sensitization.

NPSp responses were predictive of experimental pain but not ongoing clinical pain intensity, consistent with work showing that medial prefrontal-striatal systems rather than classic nociceptive systems are correlated with chronic low back pain.[6]

The *NPSn pattern* includes patterns within medial regions in which greater deactivation was previously associated with increased pain.[70] In this study, however, increased pain was associated with greater activations in healthy participants (specifically for the PCC/precuneus cluster) and patients with

FM (for both the PCC/precuneus and the pgACC clusters). The pgACC showed increased activation specifically for patients with FM, in agreement with previous findings showing that chronic pain patients do not deactivate pgACC/medial PFC and/or surrounding regions of the "default mode" network as strongly as controls do (and sometimes show activation).[2,5,6,12,27,63,72] Conversely, the PCC/precuneus may activate in response to pressure-evoked pain in both healthy[4,16,43,65] and patient populations.[27,48,59,65] The value of "default mode" network regions as predictors of pain may therefore vary across pain modalities and pain patient groups. We discuss the issue in detail in Supplementary Text 3 (available online at http://links.lww.com/PAIN/A340).

The *FM-pain pattern* complements the NPS results by showing that FM was best characterized by concurrently augmented pain-evoked activation in regions that show an important role in sensory integration (anterior SII extending to middle insula) and "default mode" regions and reduced activation of the dorsolateral PFC, a region commonly found to play a role in pain and emotion regulation.[71,73] This pattern, which was (together with the multisensory) predictive of clinical pain in patients, also emphasizes the importance of some key regions that are not part of the NPS (and are important for self-related, motivational, and emotional regulation) as targets for future study in FM.

Supplementary analyses of medication use indicated that it was not sufficient to explain the relationship between the status of patients with FM and alterations in brain activity (Supplementary Text 4, available online at http://links.lww.com/PAIN/A340).

The *multisensory pattern* is the feature that most strongly discriminates patients with FM from healthy participants, with and without controlling for NPS and FM-pain responses, and contributes to predict clinical pain. Central processing of nonpainful sensory signals may be of particular importance in maintaining clinical pain in FM, in agreement with previous work.[29,42,58] Consistently, Harte et al.[29] very recently showed that fMRI data during a visual task could discriminate patients with FM vs healthy controls with 82% accuracy. The multisensory pattern shows early sensory cortical processing attenuation, which is consistent with reduced processing of fine sensory/discriminative properties of stimulus,[1,18,46,53] accompanied by amplification of sensory integration (in agreement with Ref. 29) and self-referential aspects of the response, including potential threat of harm.[17]

The FM-pain pattern could accurately classify patients vs controls using multisensory brain responses and vice versa, which may reflect a more global brain reorganization in FM that may be detected across a range of experimental conditions. Our study and others show overlapping brain functional alterations during rest and task performance in FM and other chronic pain conditions involving sensory integration (eg, Refs. 19,36,42,58), salience (Refs. 33,42,50,58,68), and default-mode network regions (eg, Refs. 6–8,49,50,58).

Overall, we have found an augmented NPSp response that is consistent with enhanced nociceptive processing, and partly mediates augmented mechanical pain, and, more broadly, evidence for central nervous system alteration in brain processing of sensory stimuli that go beyond nociception, consistent with a central nervous system pathophysiological component in FM.

Several limitations and future directions remain to be addressed in future studies. First, replication of these results with fully independent validation samples is a next step toward translational utility. The validation process is a long, multistudy, and multipublication effort.[9,26] Second, false-negative cases, ie, patients who are erroneously classified as healthy controls using these brain measures, are always a possibility. Importantly, these brain patterns may not capture other sensory/affective/cognitive processes that may also be altered in patients with FM. Third, the brain pattern–symptom severity correlations that we present are preliminary and need replication in multiple samples. Fourth, further studies are needed to test whether our findings generalize to other chronic pain populations or are specific to FM. Last, all participants included in the study were females and therefore the findings cannot be generalized to the population of men with FM, for which future generalization and validation studies are warranted.

Overall, an important open question concerns the extent to which FM and other chronic pain disorders are pathophysiologically distinct or may share certain brain features independent of primary etiology. Testing the generalizability of the brain patterns we identify here may advance our understanding regarding the common and independent central pathophysiology of distinct chronic pain conditions across domains of sensory processing. Thus, the current approach may help in identifying pain endophenotypes across a spectrum of chronic pain conditions and in providing objective guidance for therapeutic interventions on an individualized basis.

Conflict of interest statement

The authors declare no conflict of interests.

Appendix A. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A340.

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