

# Pharmacologic attenuation of cross-modal sensory augmentation within the chronic pain insula

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## Abstract

Pain can be elicited through all mammalian sensory pathways yet cross-modal sensory integration, and its relationship to clinical pain, is largely unexplored. Centralized chronic pain conditions such as fibromyalgia are often associated with symptoms of multisensory hypersensitivity. In this study, female patients with fibromyalgia demonstrated cross-modal hypersensitivity to visual and pressure stimuli compared with age- and sex-matched healthy controls. Functional magnetic resonance imaging revealed that insular activity evoked by an aversive level of visual stimulation was associated with the intensity of fibromyalgia pain. Moreover, attenuation of this insular activity by the analgesic pregabalin was accompanied by concomitant reductions in clinical pain. A multivariate classification method using support vector machines (SVM) applied to visual-evoked brain activity distinguished patients with fibromyalgia from healthy controls with 82% accuracy. A separate SVM classification of treatment effects on visual-evoked activity reliably identified when patients were administered pregabalin as compared with placebo. Both SVM analyses identified significant weights within the insular cortex during aversive visual stimulation. These data suggest that abnormal integration of multisensory and pain pathways within the insula may represent a pathophysiological mechanism in some chronic pain conditions and that insular response to aversive visual stimulation may have utility as a marker for analgesic drug development.

**Keywords:** Multisensory hypersensitivity, Fibromyalgia, Pregabalin, Functional magnetic resonance imaging, Quantitative sensory testing, Visual system, Machine learning

## 1. Introduction

Pain is an unpleasant sensory phenomenon that can be evoked from multiple stimulus modalities. Sounds, lights, temperatures, odors, and tactile stimuli all can evoke unpleasant reactions and painful sensations. While pain is typically initiated by the stimulation of receptors in the periphery, augmentation and attenuation of afferent signals occur in the spinal cord and brain, where the perception of pain is ultimately experienced.<sup>56,68</sup>

Many patients with chronic pain report symptoms related to multisensory hypersensitivity, including to sensations that bypass

spinal pathways (eg, lights are bright, odors are bothersome). As an exemplar, migraineurs experience exacerbation of headache by visual stimuli.<sup>27,52</sup> Quantitative sensory testing suggests that there may be a central nervous system (CNS)-mediated global sensory disturbance that contributes to the pathophysiology of many chronic pain states, as well as other conditions with sensory dysfunction (eg, hyperacusis, multiple chemical sensitivity, autism).<sup>10,28,29,37,40,53,73</sup> While the origin of this aberrant sensory processing is unknown, the insula could be one such locus. The insula has been proposed as a higher order sensory processing region<sup>16,17,67</sup> with demonstrated altered activity in chronic pain.<sup>7,11,13,43,59</sup>

Fibromyalgia is a chronic pain condition showing insular hyperactivity. While peripheral factors may contribute to the pain experienced by some patients with fibromyalgia,<sup>60</sup> there is substantial evidence for CNS dysfunction in this and related “centralized” pain states. Specifically, patients with fibromyalgia exhibit changes in gray matter volume,<sup>12</sup> elevations in excitatory and reductions in inhibitory neurotransmitters,<sup>26,35</sup> altered connectivity to various brain networks,<sup>58,59</sup> and enhanced response to experimental stimuli<sup>20,47,48,51</sup> within the anterior and posterior insula.<sup>20,47,48,51</sup> Recently, pharmacologic treatment with pregabalin, a compound shown to be efficacious in fibromyalgia,<sup>19,25</sup> rectified aberrant insular neurochemistry and connectivity.<sup>34</sup> These data have led some to propose that a central sensory gain in part driven by insular hyperactivity plays a prominent role in fibromyalgia, and more generally, in chronic pain.<sup>15,73</sup>

While patients with fibromyalgia are well known to be hypersensitive to painful somatic mechanical and thermal stimulation,<sup>45,62,63</sup> hypersensitivity also exists to non-painful auditory and visual stimuli.<sup>28,40,51,54,76</sup> These latter findings suggest that

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fibromyalgia pain may be related to generalized sensory amplification. Interestingly, functional magnetic resonance imaging (fMRI) studies of pain suggest insular involvement in multisensory processing and integration.<sup>51,57</sup>

In this study, we investigated associations between visual stimulus-evoked unpleasantness, experimental and clinical pain, and their subsequent brain responses in patients with fibromyalgia as compared with healthy controls. We hypothesized that patients with fibromyalgia would report increased unpleasantness to visual stimulation and that this response would be associated with augmented insular activation. We reasoned that cross-modal correlations between visual-evoked unpleasantness and pressure pain sensitivity would be observed. Furthermore, we hypothesized that visually evoked brain activity would be associated with clinical pain, if both are integrated within a common locus. Finally, we used support vector machines (SVM) to demonstrate the utility of fMRI data derived from visual stimulation to predict whether a participant was either a patient with fibromyalgia or a healthy control, and furthermore, whether a patient was administered pregabalin or placebo, thus potentially making this measure useful in the development of new centrally acting pharmacologic therapies for centralized pain states.

## 2. Material and methods

### 2.1. Participants

This study was approved by the medical Institution Review Board at the University of Michigan, and all participants read and signed an informed consent form prior to participation. Inclusion criteria for the patients with fibromyalgia were as follows: (1) satisfaction of the 1990 American College of Rheumatology criteria for fibromyalgia,<sup>77</sup> (2) disease duration of >6 months, (3) willingness to not introduce any new fibromyalgia treatments for the duration of the study, (4) 18–75 years of age, (5) right-handed, (6) self-reported clinical pain  $\geq 40$  mm on a 100-mm pain visual analog scale (VAS) at the time of enrollment, and (7) capable of giving informed consent. Exclusion criteria included (1) current use or history of taking opioid or narcotic analgesics, sedatives, hypnotics, unstable doses of antidepressants, non-steroidal anti-inflammatory drugs, or muscle relaxants due to the potential modulation of brain activity produced by these compounds,<sup>34,42,49,69</sup> (2) history of substance abuse or positive urine drug screen for drugs of abuse, (3) concurrent autoimmune or inflammatory disease that causes pain, such as rheumatoid arthritis, systemic lupus, erythematosus, or inflammatory bowel disease, (4) concurrent participation in other therapeutic trials or treatment with an investigational drug within 30 days of enrollment, (5) pregnant or currently nursing, (6) psychiatric illness (eg, current schizophrenia, major depression with suicidal ideation, or substance abuse within the past 2 years), (7) contraindications with fMRI procedures, and (8) pain due to other conditions (eg, migraine headaches) that could confound fibromyalgia pain. For the subset of patients with fibromyalgia who received pregabalin, an additional exclusion criteria was previous unresponsiveness to pregabalin treatment of  $\geq 300$  mg/d.

Healthy control participants were age- and sex-matched to the patients with fibromyalgia. Inclusion criteria for healthy controls were as follows: (1) 18–75 years of age, (2) right-handed, (3) capable of giving written informed consent, and (4) willingness to complete all study procedures. Exclusion criteria for the healthy control participants were as follows: (1) satisfaction of the 1990 American College of Rheumatology fibromyalgia criteria, (2) any

chronic medical illness, including psychiatric disorders (eg, psychosis, schizophrenia, delusional disorder), (3) diagnosed with a chronic pain disorder, (4) current pregnancy, and (5) contraindications with fMRI procedures.

In total, 62 participants were included in this study (42 patients with fibromyalgia, 20 healthy controls). A behavioral session consisting of a visual stimulation task and pressure pain testing was completed by 25 patients with fibromyalgia and 20 healthy control participants. In addition, 28 patients with fibromyalgia and 19 healthy controls underwent fMRI with this visual task. From this group, a subset of 17 patients with fibromyalgia also participated in a pharmacological intervention study with pregabalin. Data from these 17 patients with fibromyalgia were reported previously in a publication examining the effects of pregabalin on brain glutamate levels, resting connectivity patterns, and response to evoked experimental pain.<sup>34</sup> The entire list of participants and which arm of the study each participant completed can be found in Supplementary Table 1 (available online as Supplemental Digital Content at <http://links.lww.com/PAIN/A266>).

## 2.2. Behavioral data

### 2.2.1. Demographics and clinical pain

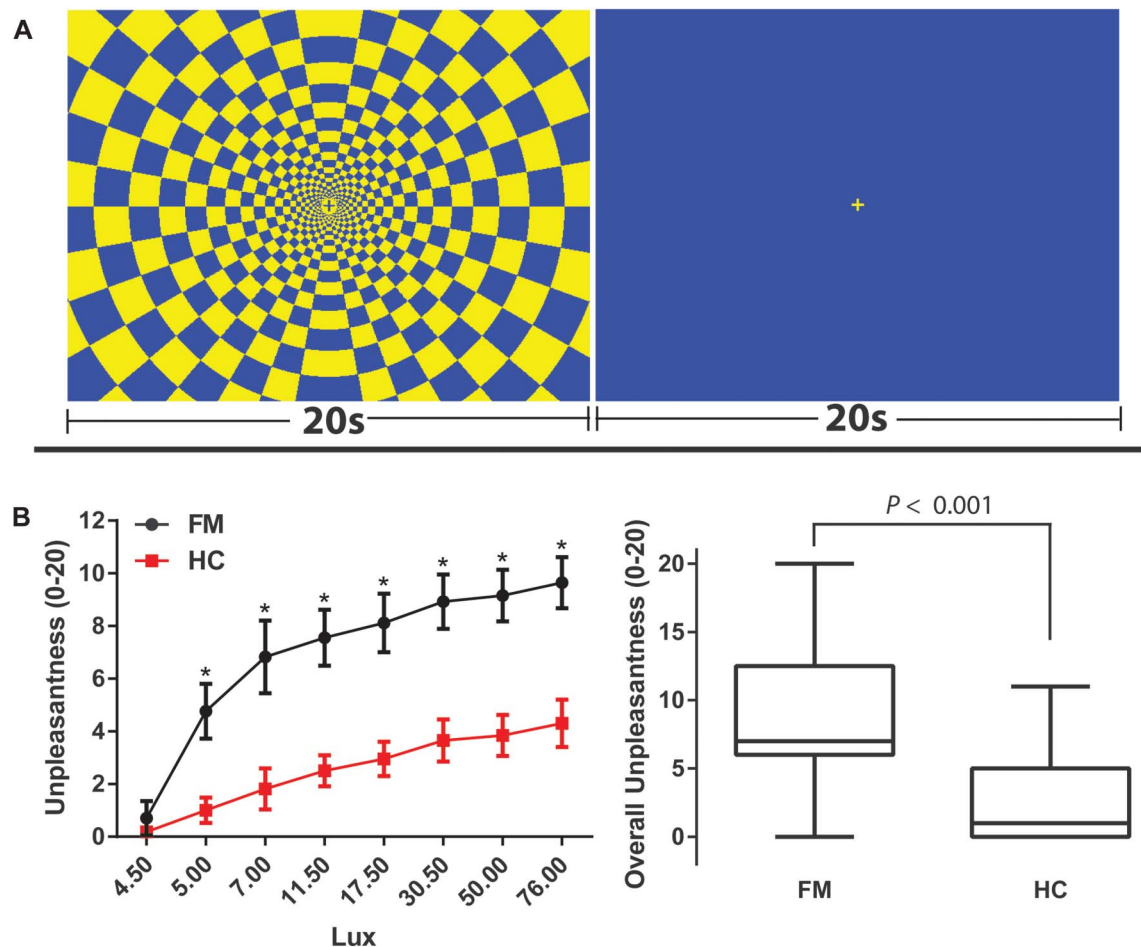
A standardized form was used to record age and medical history. Participants reported their current clinical pain intensity using a 100-mm VAS anchored by “0” labeled as “no pain” and “100” labeled as “worst pain imaginable.”

### 2.2.2. Visual stimulation task

Participants underwent a 3-minute dynamic visual stimulation task developed in MATLAB (Mathworks, Natick, MA) that consisted of alternating 20-second blocks of a flashing (8 Hz frequency) blue-yellow annulus checkerboard and a static fixation cross (**Fig. 1A**). The checkerboard was presented at eight illumination levels in ascending order ranging from 4.5 to 76 lux and rated using the Gracely Box scale (GBS) for affective unpleasantness.<sup>63</sup> This scale lists the numbers 0 to 20 in the descending order next to a set of verbal descriptors ranging from “very intolerable” (between 17 and 18) to “neutral” (0).<sup>31</sup> Participants were asked to choose the number that best describes their affective reaction to each intensity level of the visual stimulus. In addition, participants provided a GBS rating of the overall unpleasantness evoked by the entire task at its completion. During testing, participants sat in a dark room, with their eyes perpendicularly aligned 24 inches away from a 15-inch (diagonal) LED monitor displaying the visual stimulus and the GBS. Illuminance was verified using a calibrated light meter (CEM DT-1309). Participants were allowed 1 minute for darkness acclimation prior to task start.

### 2.2.3. Experimental pressure pain

Pressure pain sensitivity was evaluated at the thumb-nail,<sup>2,30,33,38,64</sup> using the multimodal automated sensory testing (MAST) system.<sup>36,70,75</sup> The MAST system consists of a control computer that executes testing algorithms and stores testing data, and a touchscreen interface for participant feedback. Computer-controlled pressure stimuli are applied to the thumb-nail bed through a 1-cm<sup>2</sup> rubber probe housed within a wireless, pistol-grip style handset. Probe movement is driven by a miniature servomotor. A closed-looped control system measures applied pressures and dynamically self-adjusts motor output to the



**Figure 1.** Patients with fibromyalgia report increased affective unpleasantry in response to visual stimulation. (A) A dynamic visual stimulus was presented to individuals with fibromyalgia and healthy controls wherein participants viewed a 3-minute movie clip of alternating 20-second blocks of a flashing (8 Hz) blue-yellow annulus checkerboard (left panel) and a static fixation cross (right panel). The checkerboard was presented in increasing illumination levels, ranging from 4.5 to 78 lux. (B) Participants rated the unpleasantry evoked by the visual stimulus at each illumination level (left panel), and the overall unpleasantry of the entire visual task (right panel). FM = patients with fibromyalgia; HC = healthy control participants. \*Significant pairwise comparisons.

resistance of the thumb and any movement to ensure accurate and repeatable force delivery.

Participants received scripted instructions and underwent MAST training and practice testing prior to data collection. During testing, an ascending series of 5-s duration pressures were delivered at a ramp rate of  $4 \text{ kg}^{-1} \cdot \text{cm}^{-2} \cdot \text{s}^{-1}$  to the dominant thumbnail beginning at  $0.50 \text{ kg/cm}^2$  and increasing in  $0.50 \text{ kg/cm}^2$  steps, with a minimum interstimulus interval of 20 seconds. Pain intensity was rated after each stimulus on a 0 to 100 numerical rating scale displayed on the interface screen (0 = no pain; 100 = worst pain imaginable). Testing terminated when the first of the three possible stop conditions was met: (1) participant reached her personal pain tolerance and requested to stop the test, (2) patient reported a pain intensity rating of  $>80/100$ , or (3) the maximum pressure of  $10 \text{ kg/cm}^2$  was delivered. A linear model was used to fit the stimulus-response data obtained from this procedure and interpolate *Pain*<sub>50</sub>, defined as the pressure intensity that evokes a moderate level of suprathreshold pressure pain (ie, 50/100). Additional derived variables included (1) pressure pain threshold, defined as the first pressure in a series of at least 2 consecutive pressures that elicited a numerical rating scale pain rating  $>0$ ; (2) *slope* of the stimulus-response function as a measure of the rate of pain increase; (3) pressure pain *tolerance*, defined as the last pressure recorded in the

stimulus-response profile; and (4) pain sensitivity range (PSR), the absolute difference between tolerance and threshold.

### 2.3. Functional magnetic resonance imaging data acquisition

Of the enrolled participants, 28 patients with fibromyalgia and 19 healthy control participants underwent a baseline fMRI session with the visual task. Data were collected using 2 different magnetic resonance scanners: a General Electric 3.0 Tesla Signa Scanner 9.0, VH3 with a quadrature birdcage transmit-receive radio frequency coil ( $n = 23$  participants; fibromyalgia:  $n = 19$ , healthy control:  $n = 4$ ), and a General Electric 3.0 Tesla MR 750 Discovery Scanner, DV23.1\_VO2\_1317.c with a quadrature birdcage transmit-receive radio frequency coil ( $n = 24$  participants; fibromyalgia:  $n = 9$ , healthy control:  $n = 15$ ). The same scanner was used throughout the study for individuals who underwent multiple scans. The visual task fMRI scan sequence was acquired with a T2\* reverse spiral gradient echo sequence (repetition time = 2500 milliseconds, echo time = 30 milliseconds, 90-degree flip angle, field of view = 22 cm). Slices were 3-mm thick, with an in-plane resolution of  $3.125 \times 3.125 \text{ mm}$ , acquired at 48 locations parallel to the anterior-posterior commissure plane. The visual task was an fMRI block design,

similar to the behavioral task, which included alternating 20-seconds blocks of a flashing blue-yellow annulus checkerboard (8 Hz frequency) and a static fixation cross. During fMRI, visual stimulus intensity remained fixed at 76 lux, and participants were asked to keep their eyes open and their attention focused on the screen.

Physiologic data for the visual task was collected simultaneously with fMRI data. Respiratory volume data were collected by securing a General Electric magnetic resonance compatible chest plethysmograph around each subject's abdomen. Cardiac data were collected using an infrared pulse oximeter attached to the subject's right middle finger. Participants' motion was minimized using foam pads placed around the head along with a forehead strap. In addition, high-resolution structural images were acquired with the following sequence: repetition time = 10.5 milliseconds per echo time = 3.4 milliseconds, inversion time = 200 milliseconds, 25-degree flip angle, field of view = 24 cm, 256 × 256 matrix, 0.94 × 0.94 × 1.5 mm voxels, yielding 106 slices using spoiled gradient echo inversion recovery sequences. Inspection of individual T1 MR images revealed no gross morphological abnormalities for any patient or control.

## 2.4. Pharmacological intervention

A subset of the patients with fibromyalgia ( $n = 17$ ) who underwent fMRI were enrolled in a double-blind, 2-period, crossover study of pregabalin vs placebo.<sup>34</sup> In brief, patients who were randomized to pregabalin for period 1 underwent dose escalation of pregabalin to 450 mg/d over the course of 14 days and were maintained at that fixed dose for the last 3 days of treatment. Those randomized to placebo for period 1 took matching placebo pills over the course of 14 days. After period 1, all patients underwent a 7-day taper and 8 days of placebo treatment for washout. Following washout, patients crossed over to the other treatment for period 2. Before and after pregabalin and placebo periods (pretreatment and posttreatment time points), patients underwent the fMRI visual task. Clinical pain was assessed by VAS immediately prior to each fMRI session. Imaging data were stored, validated, analyzed, and assessed for quality at the University of Michigan independently of Pfizer personnel. Clinical data were double-entered, quality checked, and databases were locked before analysis. Full results are reported at clinicaltrials.gov (NCT01057693).

## 2.5. Data analysis

### 2.5.1. Behavioral data (outside of magnetic resonance imaging environment)

Within and between-group differences in visual stimulus unpleasantness ratings were assessed using a linear mixed model. The linear mixed model included group (2 levels: healthy control and fibromyalgia) and illuminance (8 levels: 4.5, 5, 7, 11.5, 17.5, 30.5, 50, and 76 lux) as fixed effects and controlled for within-subject variation in responses to visual stimulation by including random effects for participants, with a variance components covariance structure and restricted maximum likelihood estimation. Pairwise comparisons with Bonferroni correction were performed for group differences at each illuminance level. Planned comparisons by independent samples  $t$  tests (2-tail) were used to evaluate group differences in age, clinical pain, and pressure pain sensitivity. Independent variables following a non-normal distribution, as determined by the Shapiro–Wilk test, were compared using the Mann–Whitney  $U$  test. Associations between

visual unpleasantness and clinical pain intensity (VAS) were examined by Spearman rho ( $r_s$ ) rank-order correlations to accommodate normality violations within the behavioral data set. All analyses were conducted using SPSS 22 (IBM, Armonk, NY) with alpha set at 0.05.

### 2.5.2. Functional magnetic resonance imaging data

Neuroimaging data were preprocessed and analyzed using FMRIB Software Library ([www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)) and Statistical Parametric Mapping (SPM) software packages, version 8 (Functional Imaging Laboratories, London, United Kingdom) running on MATLAB 7.5b (Mathworks, Sherborn, MA). Upon collection of the functional data, cardiorespiratory artifacts were corrected for using the RETROICOR algorithm in FMRIB Software Library. Preprocessing steps included motion correction (realignment to the first image of the time series), normalization to the Montreal Neurological Institute average brain included in the SPM software (generating 2 × 2 × 2-mm resolution images), and smoothing (convolution with an 8 mm full-width at half maximum Gaussian Kernel). Subject head motion was assessed by evaluating 3 translations and 3 rotations for each scan. Translational thresholds were set to ±2 mm, whereas rotational thresholds were limited to ±1°. Participants were excluded from the analysis if head motion exceeded either of the thresholds in one of the 6 dimensions. A general linear model was constructed with parameters corresponding to the flashing annulus checkerboard and static fixation blocks, respectively. Low frequency signal fluctuations were removed with a high-pass filter of 1/128 Hz. Contrast images were then calculated by applying a linear contrast of the parameter estimates of the checkerboard vs the static fixation condition for each participant. To compare groups, an independent samples  $t$  test was performed using a general linear model in SPM. As the insula was an a priori region of interest, significance was determined by correcting for multiple comparisons on the cluster level using a familywise error (FWE), small volume correction (SVC) of  $P < 0.05$ , and voxelwise  $P < 0.001$ , created by a sphere with a 10-mm radius, built around peak voxels of previously published results.<sup>59</sup> Blood-oxygen-level-dependent (BOLD) activation responses were extracted, corrected for age and scanner, and then analyzed in SPSS with an independent samples  $t$  test and plotted to attempt to identify any outliers. Significant BOLD values were then correlated (Pearson  $r$ ) with present VAS clinical pain ratings in SPSS. Correlation results were deemed significant at  $P < 0.05$ .

### 2.5.3. Pharmacological functional magnetic resonance imaging data

We also explored the effects of pregabalin on visual stimulus-evoked brain activation. We used a whole brain search for regions showing changes in visual stimulation-related activity specifically following pregabalin. Evoked visual stimulation data were preprocessed and a general linear model was created using the same steps previously described in the evoked visual stimuli fibromyalgia vs healthy control analysis. In this analysis, pregabalin and placebo periods were compared using paired  $t$  tests in SPM to assess changes in visual associated BOLD signals. To specifically contrast differences between pregabalin and placebo periods, a flexible factorial analysis including pretreatment and posttreatment scans for both periods were performed in SPM. Results were deemed significant using an FWE cluster level-corrected threshold of  $P < 0.05$  based on a voxelwise threshold of  $P < 0.001$  uncorrected. Multiple regression analyses were also

performed in SPM correlating changes in present VAS clinical pain report (post–pre) with changes in BOLD activity (post–pre) following pregabalin or placebo administration.

#### 2.5.4. Support vector machine classification

A multivariate pattern analysis (MVPA) approach using SVM was used to investigate the predictive utility of the visual stimulus to classify a study participant either as a patient with fibromyalgia or a healthy control. Support vector machine learning was performed using the libsvm toolbox version 3.18<sup>14</sup> in MATLAB 7.5b, using the contrast images for each subject, labeled by cohort (fibromyalgia or healthy control). Support vector machine classification was performed using a linear kernel, with 5-fold cross-validation for C parameter optimization in the training data, and leave-one-subject-out cross-validation in the testing data to calculate accuracies and predicted values. Support vector machine model weights were averaged across all leave-one-subject-out instances to investigate spatial distribution of the weights. Permutation testing was performed to generate significant levels for the model weights, by permuting the treatment labels 100 times for each leave-one-out instance, resulting in 1700 model weight instances for each voxel location, allowing significance to be calculated by the number of times a model weight occurred in the histogram. Significant values were overlaid on reference anatomy, and the contrast values of the most significant areas were plotted to examine their relationship to the multivariate pattern.

Subsequent SVM analyses were performed to predict treatment type using visual-evoked fMRI data in the patients with fibromyalgia who underwent pharmacologic intervention. Previously described contrast images were acquired for each subject and entered into the *imcalc* function in SPM to create “posttreatment minus pretreatment” difference images (eg, subtracting

a pre-pregabalin contrast image from a post-pregabalin contrast image results in a difference image for the pregabalin treatment period) for both the pregabalin and placebo treatment arms. One SVM analysis was performed using the difference contrast images for each subject, labeled by treatment (pregabalin or placebo) and conducted as described above, except both the pregabalin and placebo conditions were left out for that one subject. The second SVM analysis was performed to investigate whether the significant brain region weights previously identified between patients with fibromyalgia and healthy controls could accurately predict treatment response (pregabalin or placebo) to aversive visual stimulation. We applied weight maps from the above cross-sectional fibromyalgia vs healthy control SVM classification to calculate the accuracies and predicted values for treatment response.

### 3. Results

#### 3.1. Patients with fibromyalgia exhibit cross-modal hypersensitivity to visual and pressure stimuli

A total of 42 female patients with fibromyalgia (mean  $\pm$  SD: 40.9  $\pm$  10.7 years) and 20 age-matched healthy females (41.4  $\pm$  11.7 years) were enrolled (Table 1 and Supplementary Table 1, available online as Supplemental Digital Content at <http://links.lww.com/PAIN/A266>). As expected, patients with fibromyalgia reported significantly greater clinical pain than healthy control participants (VAS: fibromyalgia = 48.2  $\pm$  23.3, healthy control = 0.85  $\pm$  2.50,  $P < 0.001$ ; Table 1). Given that different subgroups of patients with fibromyalgia were used in different analyses, we compared age and self-reported clinical pain values (VAS) across fibromyalgia subgroups with one-way analysis of variance; no significant differences in age ( $P = 0.814$ ) or clinical pain ( $P = 0.556$ ) were observed (Supplementary Table 1, available online as

**Table 1**  
Age, clinical pain, and responses to experimental sensory stimulation.

	FM (n = 42)*	HC (n = 20)	P
Age (y)	40.9 $\pm$ 10.7	41.4 $\pm$ 11.9	0.858
VAS (at baseline)	48.2 $\pm$ 23.3	0.85 $\pm$ 2.50	<b>&lt;0.001</b>
Visual unpleasantness rating (4.5 lux)	0.71 $\pm$ 2.66	0.18 $\pm$ 0.60	0.955
Visual unpleasantness rating (5.0 lux)	4.76 $\pm$ 4.30	1.00 $\pm$ 1.61	<b>0.019</b>
Visual unpleasantness rating (7.0 lux)	6.82 $\pm$ 5.71	1.82 $\pm$ 2.60	<b>0.002</b>
Visual unpleasantness rating (11.5 lux)	7.56 $\pm$ 5.34	2.50 $\pm$ 2.65	<b>&lt;0.001</b>
Visual unpleasantness rating (17.5 lux)	8.12 $\pm$ 5.58	2.95 $\pm$ 2.91	<b>&lt;0.001</b>
Visual unpleasantness rating (30.5 lux)	8.92 $\pm$ 5.18	3.65 $\pm$ 3.59	<b>&lt;0.001</b>
Visual unpleasantness rating (50.0 lux)	9.16 $\pm$ 4.90	3.85 $\pm$ 3.53	<b>&lt;0.001</b>
Visual unpleasantness rating (76.0 lux)	9.64 $\pm$ 4.90	4.30 $\pm$ 4.03	<b>&lt;0.001</b>
Mean visual unpleasantness rating	7.40 $\pm$ 4.55	2.95 $\pm$ 2.78	<b>0.001</b>
Overall visual task unpleasantness	8.71 $\pm$ 5.29	2.75 $\pm$ 3.06	<b>&lt;0.001</b>
PPT	1.00 $\pm$ 0.61	1.35 $\pm$ 1.26	0.552
Pain50	2.74 $\pm$ 1.09	4.11 $\pm$ 3.36	<b>0.044</b>
Tolerance	3.68 $\pm$ 1.13	4.80 $\pm$ 1.62	<b>0.020</b>
Slope	27.32 $\pm$ 9.66	21.12 $\pm$ 9.58	<b>0.047</b>
PSR	2.68 $\pm$ 0.85	3.45 $\pm$ 0.94	<b>0.006</b>

Data presented as means  $\pm$  SD.

Significant group comparisons are in bold text.

\* n = 25 for behavioral assessments.

FM, patient with fibromyalgia; HC, healthy control participant; PPT, pressure pain threshold; PSR, pain sensitivity range; VAS, visual analog scale.

Supplemental Digital Content at <http://links.lww.com/PAIN/A266>. A subset of 25 patients with fibromyalgia ( $41.6 \pm 10.7$  years) and all 20 healthy control participants ( $41.4 \pm 11.9$  years) participated in a behavioral testing session consisting of visual stimulation presented at 8 illumination levels (**Fig. 1A**) and pressure pain sensitivity testing. Both patients with fibromyalgia and healthy control participants exhibited a stimulus-dependent increase in unpleasantness evoked by visual stimulation, such that unpleasantness ratings increased as light intensity increased; however, patients with fibromyalgia reported significantly greater unpleasantness ratings than healthy control participants. Using a linear mixed model, significant main effects were found for visual stimulus illuminance ( $F_{(7,250.5)} = 36.53, P < 0.001$ ) and group ( $F_{(1,43.38)} = 13.35, P = 0.001$ ), with a significant illuminance  $\times$  group interaction ( $F_{(7,250.5)} = 5.66, P < 0.001$ ). The mean unpleasantness rating of the visual task (collapsed across 8 illumination levels) was significantly greater in patients with fibromyalgia than in controls ( $P < 0.001$ ; **Table 1**). Significant pairwise comparisons between groups showed greater unpleasantness ratings from patients with fibromyalgia at all illumination levels except the lowest (**Table 1, Fig. 1B left**). At the completion of testing, the visual task was rated overall as more unpleasant by patients with fibromyalgia relative to healthy controls (fibromyalgia =  $8.71 \pm 5.29$ , healthy control =  $2.75 \pm 3.06, P < 0.001$ ; **Table 1, Fig. 1B right**).

Consistent with the previous work from our laboratory, patients with fibromyalgia also exhibited increased pressure pain sensitivity at the thumbnail compared with healthy control participants as indicated by several different psychophysical metrics: Pain50, pressure pain tolerance, slope of the stimulus–response function, and PSR (**Table 1**). Pressure pain threshold however was not significantly different between groups (**Table 1**).

The relationship between visual stimulus unpleasantness and evoked pressure pain was further explored in patients with fibromyalgia (**Table 2**). Significant negative correlations were observed between overall unpleasantness of the visual task and pressure pain tolerance ( $r_s = -0.41, P = 0.047$ ) and PSR ( $r_s = -0.471, P = 0.02$ ); a trend was observed for Pain50 ( $r_s = -0.388, P = 0.061$ ). Positive correlations were found with slope of the pressure pain stimulus–response curve and overall visual task unpleasantness ( $r_s = 0.468, P = 0.021$ ) and mean visual stimulation unpleasantness rating ( $r_s = 0.524, P = 0.007$ ). These findings suggest that increased unpleasantness to visual stimulation is associated with increased somatic pain sensitivity,

and moreover, that sensitivity to visual and pressure stimuli may have a common pathological substrate in fibromyalgia. Consistent with this finding, patients with fibromyalgia also showed a significant correlation between clinical pain (measured by VAS) and overall visual task unpleasantness ( $r_s = 0.483, P = 0.020$ ; **Table 2**), such that greater pain intensity was related to increased negative affect in response to experimental visual stimulation. Of note, weak but nonsignificant correlations between visual task unpleasantness and pressure pain tolerance and Pain50 were observed in healthy control participants (not shown), suggesting that the integration of these modalities may be enhanced preferentially in the chronic pain brain.

### 3.2. Visual stimulus-evoked brain activation differs between patients with fibromyalgia and healthy controls

Twenty-eight patients with fibromyalgia ( $39.7 \pm 11.2$  years) and 19 healthy control participants ( $41.1 \pm 12.2$  years) participated in an fMRI session with the same visual task but held constant at the highest illumination level (76 lux). All participants' data passed quality assessment and were included for analysis, except for 3 subjects: 1 healthy control participant with poor image quality, 1 patient with fibromyalgia with poor image quality, and 1 patient with fibromyalgia who did not complete the task in the MRI scanner. When comparing brain responses to visual stimulation, the fibromyalgia group showed greater activation in the right anterior insular cortex during the visual stimulus than healthy control participants (peak voxel:  $x = 45, y = 21, z = 5; 464 \text{ mm}^3; z = 3.59, P = 0.009$ , SVC ( $x = 42, y = 14, z = 8$ ); **Fig. 2A**). When controlling for participant age and scanner, increased right anterior insular activation in patients with fibromyalgia remained significant compared with healthy control participants ( $P = 0.022$ ; **Fig. 2A**). In patients with fibromyalgia, there was a significant correlation between right anterior insular activation during visual stimulation and VAS pain ( $r = 0.450, P = 0.016$ ; **Fig. 2B**), wherein greater insular activation was associated with increased clinical pain intensity.

### 3.3. Pregabalin attenuates visual stimulus-evoked brain activation

A subset of 17 patients with fibromyalgia who underwent fMRI participated in our previously reported pregabalin study.<sup>34</sup> Paired sample *t* tests comparing before and after pregabalin treatment on evoked visual brain activity revealed a decrease in bilateral anterior insular activation following treatment (right anterior insular peak voxel:  $x = 42, y = 20, z = 4; 5968 \text{ mm}^3; z \text{ score} = 5.44, P_{\text{FWE}} < 2.0 \times 10^{-6}$ ; left anterior insular peak voxel:  $x = -46, y = 14, z = 2; 728 \text{ mm}^3; z \text{ score} = 3.87, P = 0.002$ , SVC ( $x = 42, y = 14, z = 8$ ); **Fig. 3A**). No significant reductions or increases in brain response to evoked visual stimulation were found following placebo treatment. To directly compare drug and placebo differences in the visual task, we performed a flexible factorial analysis in SPM. The pregabalin arm resulted in a greater reduction in right anterior insular activation during the visual stimulus than in placebo (peak voxel:  $x = 50, y = 8, z = 2; 4872 \text{ mm}^3; z \text{ score} = 4.45, P_{\text{FWE}} = 0.0004$ ; **Fig. 3B**).

### 3.4. Support vector machine classification of visual stimulus-evoked functional magnetic resonance imaging data predicts patients with fibromyalgia from healthy controls

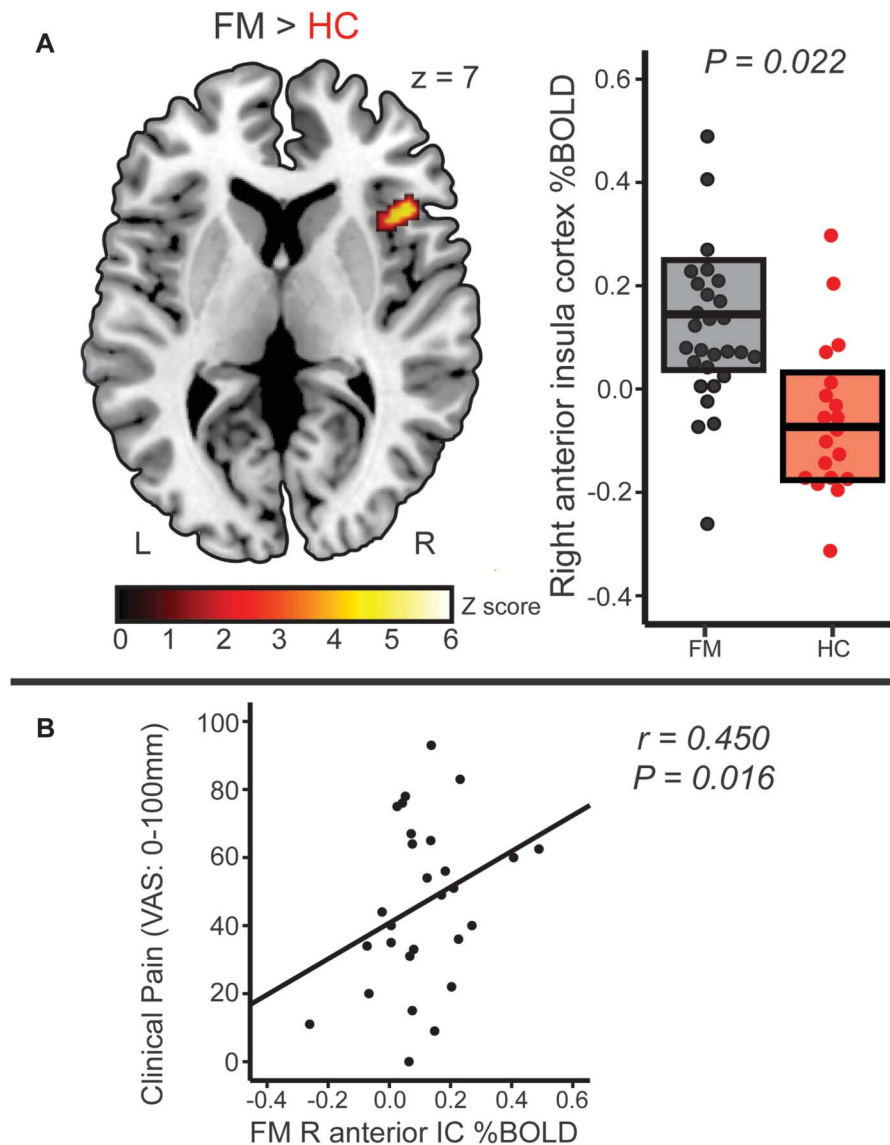
Support vector machine classification to predict cohort type was conducted using baseline visual stimulus-evoked brain activation data from 17 patients with fibromyalgia ( $39.7 \pm 10.9$  years) and

**Table 2**

**Correlations (Spearman rho) of visual stimulation unpleasantness ratings with clinical pain and pressure pain sensitivity for outcomes showing differences between groups for the 25 patients with fibromyalgia who underwent behavioral testing.**

	Overall visual unpleasantness		Mean visual unpleasantness	
	$r_s$	$P$	$r_s$	$P$
VAS	<b>0.483</b>	<b>0.020</b>	0.374	0.072
Tolerance	<b>-0.410</b>	<b>0.047</b>	-0.372	0.067
Pain50	-0.388	0.061	-0.384	0.058
Slope	<b>0.468</b>	<b>0.021</b>	<b>0.524</b>	<b>0.007</b>
PSR	<b>-0.471</b>	<b>0.020</b>	-0.375	0.065

PSR, pain sensitivity range; VAS, visual analog scale for clinical pain. Significant correlations are in bold text.



**Figure 2.** Increased brain activation in response to aversive visual stimulation is associated with clinical pain intensity in fibromyalgia. (A) Individuals with fibromyalgia (FM) displayed greater functional magnetic resonance imaging blood–oxygen–level–dependent (BOLD) activations in right anterior insula than healthy controls (HC) during the presentation of a dynamic visual stressor. (B) Within the FM group, anterior insular activation was positively correlated with the degree of clinical pain measured using a 100-mm visual analog scale (VAS). IC, insular cortex.

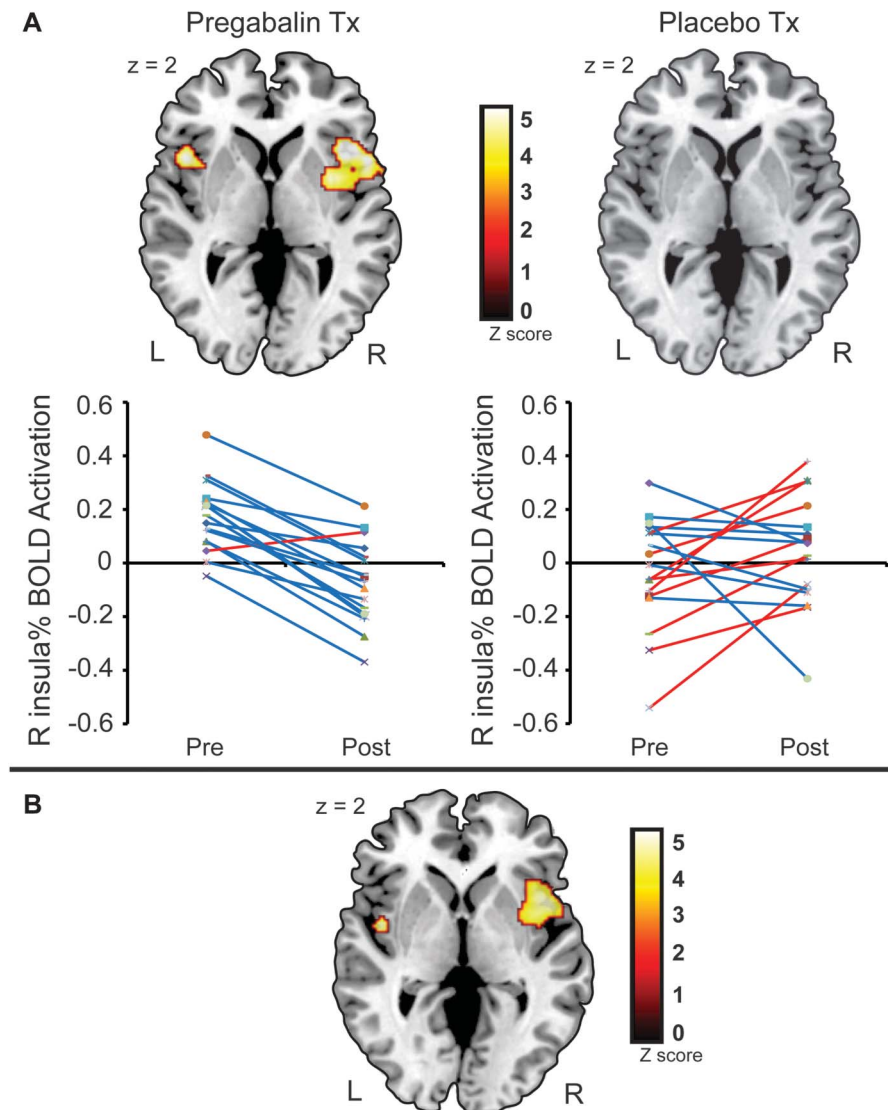
17 healthy controls ( $41.1 \pm 11.5$  years). Overall SVM accuracy for distinguishing patients from controls during the presentation of an aversive visual stimulus was 82% with 82% sensitivity and 82% specificity (**Fig. 4A**). Significant weights were observed in bilateral posterior cingulate and right posterior insular cortices (**Fig. 5A**).

### 3.5. Support vector machine classification of visual stimulus-evoked functional magnetic resonance imaging data predicts pregabalin vs placebo administration in fibromyalgia

Support vector machine classification was then used in the same seventeen patients with fibromyalgia as in the previous analysis to predict treatment effects (pregabalin vs placebo) on visual stimulus-evoked brain activation. Support vector machine classification resulted in 82% overall accuracy in distinguishing pregabalin vs placebo administration during aversive visual stimulation (**Fig. 4B**). Within each treatment condition, there

was 76% sensitivity for pregabalin and 88% for placebo. Also, individuals with incorrect placebo predictions (participant IDs: fibromyalgia15 and fibromyalgia17) had smaller pregabalin prediction scalar values. The average support vector model weights are displayed in **Figure 5B**. Significant weights were observed in the anterior insular cortex (with a larger response in the right insular cortex), visual cortex, medial frontal areas, inferior parietal lobule, and cerebellum. Displayed values were thresholded at a significant level of  $P < 0.05$ ; as in any multivariate analysis, every voxel weight depends on the values in every other voxel.

A final alternative SVM approach to classify treatment response to aversive visual stimulation was performed using the significant model derived from the SVM cohort classification (section 3.4 above). In this analysis, we asked whether the same model used to classify patients with fibromyalgia vs healthy controls could also classify drug vs placebo in patients alone. Using this approach, accuracy for distinguishing pregabalin from placebo response was only 62%. However, it should be noted that both SVM



**Figure 3.** Specific attenuation of insular response to aversive visual stimulation by pregabalin. (A) A subset of 17 patients with fibromyalgia underwent aversive visual stimulation during functional magnetic resonance imaging (fMRI) both before and after pregabalin and placebo administration. After the pregabalin period, a significant reduction in bilateral insular blood–oxygen-level-dependent (BOLD) activation in response to the visual stimulus was observed (left). No reductions in insular activation were observed after placebo treatment (right). Lines denote fMRI BOLD values for each participant (pre and post drug or placebo). Blue lines represent individuals with a decrease in BOLD activity, whereas red lines denote increases in BOLD activity. (B) A direct contrast between pregabalin and placebo periods shows decreased visual stimulus-evoked BOLD response in the right insula after pregabalin treatment.

treatment analyses found significant weights within the insular cortex. Using an exploratory approach to visualize whether the insular regions identified in the SVM patient vs control classification and the successful patient pregabalin vs placebo response classification overlap, there was convergence of the 2 weights albeit at the less stringent threshold of  $P < 0.1$  (Fig. 5C).

### 3.6. Clinical pain response to pregabalin is associated with decreased brain response to visual stimulation

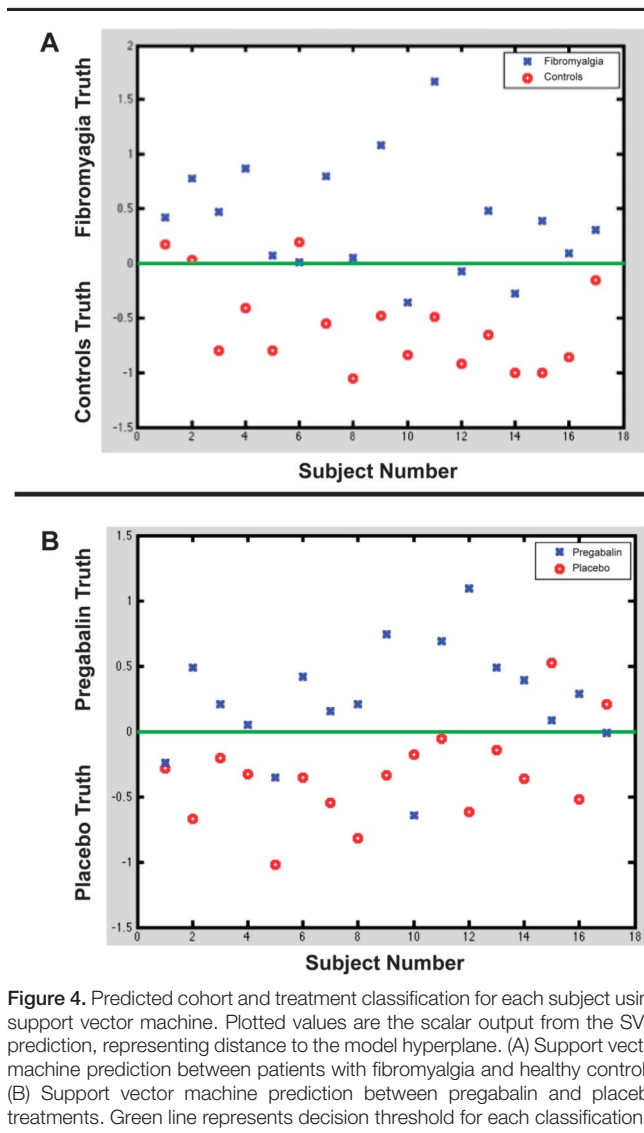
When correlating change (post – pre) in visual stimulation activation after pregabalin with change in clinical pain (post – pre), a positive correlation was found for the right anterior insula ( $r = 0.76$ ; peak voxel:  $x = 36, y = 30, z = 4$ ;  $240 \text{ mm}^3$ ;  $z \text{ score} = 3.51, P = 0.018, \text{SVC} (x = 28, y = 26, z = -6)$ ; Fig. 6A): greater reductions in clinical pain were associated with decreases in visual stimulation activation. We also detected a similar positive

correlation between the reduction in right inferior parietal lobule activation and improvements in clinical pain ( $r = 0.82$ ; peak voxel:  $x = 16, y = -60, z = 66$ ;  $5168 \text{ mm}^3$ ;  $z \text{ score} = 4.17, P_{\text{FWE}} = 0.0001$ ; Fig. 6B). No significant relationships with clinical pain changes were found during placebo treatment.

## 4. Discussion

Pain is a salient multisensory experience. In this study, we provide evidence that visual stimulus-evoked brain activity within the insula, a locus of multisensory integration, is related to pain magnitude in fibromyalgia. Insular activity in response to aversive visual stimulation was associated with greater clinical pain intensity. Moreover, attenuation of this insular activity by the analgesic pregabalin was accompanied by concomitant reductions in clinical pain. This relationship was robust as a multivariate classification method using





**Figure 4.** Predicted cohort and treatment classification for each subject using support vector machine. Plotted values are the scalar output from the SVM prediction, representing distance to the model hyperplane. (A) Support vector machine prediction between patients with fibromyalgia and healthy controls. (B) Support vector machine prediction between pregabalin and placebo treatments. Green line represents decision threshold for each classification.

visual-evoked insular activity reliably identified when patients were taking pregabalin as compared with placebo.

Patients with fibromyalgia showed increased sensitivity to pressure pain and visual stimuli compared with healthy controls. Moreover, visual distress was correlated to both pressure pain and clinical pain in patients. These findings are consistent with a growing literature demonstrating increased sensitivity to non-noxious stimuli in patients with chronic pain. Patients with fibromyalgia display increased sensitivity to auditory stimuli and rate everyday sounds as more unpleasant than controls do.<sup>10,21,28,40,55,76</sup> Similar findings have been observed in rheumatoid arthritis<sup>55</sup> and irritable bowel syndrome.<sup>4,5</sup> Recently, Martenson and colleagues reported decreased discomfort and intolerance thresholds to light stimulation in patients with fibromyalgia relative to healthy controls.<sup>54</sup> Evidence that somatic pain and nonsomatic (auditory and visual) sensitivities often correlate in patients with chronic pain,<sup>28,29,40,54</sup> reinforces our hypothesis that a global state of CNS sensory amplification may play a role in the pathogenesis of chronic pain disorders and that these sensory measures may mark an important individual patient endophenotype of centralization.<sup>15</sup>

The insula has long been known for its involvement in higher-order sensory processing. Activations of this region in response to

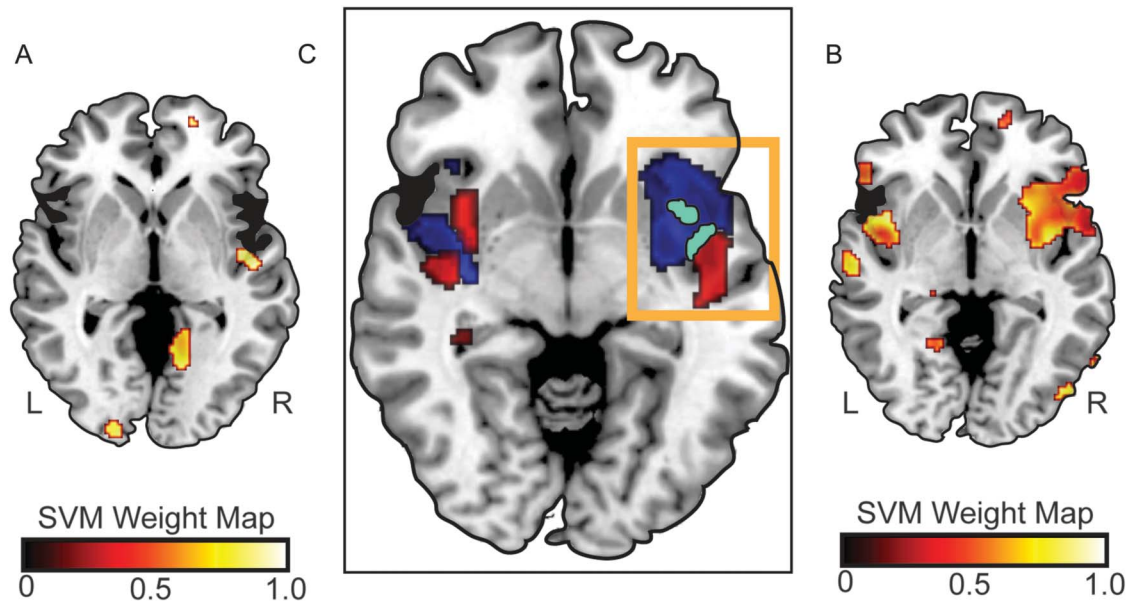
thermal,<sup>18,61</sup> auditory,<sup>57,65</sup> and olfactory<sup>50</sup> stimuli were previously reported. Unimodal and multimodal activation of the insula in response to visual stimulation and combined or changing tactile/auditory/visual stimulation has also been reported.<sup>22,23,51,57</sup> In this study, anterior insular activation in response to aversive visual stimulation overlapped with augmented brain activity previously reported in patients with fibromyalgia in response to painful mechanical stimulation applied to the body,<sup>20,48</sup> thus supporting the role of the anterior insula as a multisensory integration site. The results presented here are intriguing as the degree of insular activation in response to aversive visual stimulation was also related to the magnitude of self-reported clinical pain, which is typically described as more musculoskeletal in nature by patients with fibromyalgia. Other insular regions also appear to be involved in fibromyalgia pathology, as we found regions within the posterior insula that predicted patient vs control classification using SVM. Interestingly, the posterior insula is one of the most consistently activated regions during experimental pain in healthy controls.<sup>1,8,57,74</sup>

Multisensory integration in fibromyalgia was recently examined during fMRI using a multimodal stimulus consisting of concurrent visual, auditory, and tactile-motor components.<sup>51</sup> Compared with controls, patients with fibromyalgia displayed decreased processing in primary and secondary auditory and visual cortices, and increased activity in insular and anterior lingual cortices. Although we did not observe similar reductions in primary sensory activity with our task, both studies implicate anterior and posterior insular regions in multisensory processing. In contrast, only the anterior insula responded to visual stimulation in a sample of healthy individuals.<sup>57</sup> Whether this dual anterior and posterior insular response in fibromyalgia is a pathophysiological marker of altered multisensory integration or simply the result of different stimulation and analysis methods remains unclear.

The insula and the Default Mode Network (DMN) are also important brain regions for clinical pain. Enhanced connectivity between the insula and the DMN was observed in multiple clinical pain states.<sup>3,44,59</sup> Importantly, the degree of connectivity between the insula and this network is directly correlated with clinical pain intensity<sup>59</sup> and its amelioration.<sup>58</sup> The reduction in connectivity between the inferior parietal lobule (a region within the DMN) after treatment with pregabalin<sup>34</sup> is similar to that seen herein. We found that improvement in clinical pain during pregabalin treatment correlated with changes in evoked visual activity within the inferior parietal lobule.

Somewhat analogous findings of visual stimuli exacerbating pain have been reported in migraine.<sup>52</sup> In migraineurs, headache can be provoked by light,<sup>9</sup> and the degree of clinical pain can also be exacerbated by bright light, as well as odors and sounds.<sup>46</sup> What is relevant to the data presented here is that we excluded patients who had any history of migraine. In migraineurs, augmented activity in response to odors also includes the insula; however, other regions such as amygdala and brainstem are also involved.<sup>71</sup> Thus, while it is appealing to think that the insula may be the major higher-order multisensory integration structure, activity within other areas is also likely to be relevant.<sup>51,54</sup>

Why might multisensory integration occur in the brain and how is this related to pain? One theory is that multisensory integration improves Darwinian fitness.<sup>72</sup> An organism that detects the presence of a threat such as a predator or a noxious stimulus by parallel processing of sounds, sights, and odors can more rapidly engage its defensive repertoire than an organism that processes each stimulus in series. Thus, more efficient integration of sensory stimuli enhances survival. In contrast, as illustrated in the present data, there may be a threshold at which integration becomes



**Figure 5.** Significant support vector machine (SVM) model weights map within the insular cortex for patients with fibromyalgia compared with healthy controls, and for pregabalin vs placebo treatment classification. (A) Average weights within the insular cortex that distinguish patients with fibromyalgia from healthy controls (significance threshold at  $P < 0.05$  generated from permutation testing). (B) Average weights within the insular cortex that distinguishes pregabalin vs placebo treatment (significance threshold at  $P < 0.05$  generated from permutation testing). (C) Overlap within the insular cortex between the aforementioned analyses (significance threshold at  $P < 0.1$  generated from permutation testing for display purposes). Red denotes weights more indicative of patients with fibromyalgia from the patients vs controls classification; dark blue denotes weights more indicative of pregabalin administration from the treatment classification; light blue denotes overlap within the insular cortex between the 2 SVM analyses.

detrimental. We propose that in patients with chronic pain, specifically those that exhibit more centralized symptomology, multisensory integration may be maladaptive. Overstimulation of the sensory system through multiple inputs could introduce noise, exaggeration, and/or discordance of the senses, wherein sensory integration could be “too much of a good thing.”

Multivariate pattern analysis using SVM allows fMRI data to be placed in a prediction and classification framework that considers the full spatial pattern of brain activity and allows potential detection of multiple localized effects that may remain unidentified with conventional univariate methods.<sup>66</sup> This may be one reason why our univariate analysis of patients vs controls (**Fig. 2**) identified a somewhat different region (anterior insula) as compared with our SVM approach (posterior insula, **Fig. 5A**). Indeed, the SVM model that was derived from the patient with fibromyalgia vs control cohort classification analysis only reached 62% accuracy when applied to the pregabalin vs placebo treatment classification. This finding suggests that the same insula neurons that drive fibromyalgia pain may not be identical to those that are involved in its response to treatment (pregabalin). This relatively low prediction accuracy is also consistent with a previous MVPA study of pain perception.<sup>6</sup> Nevertheless, the accuracy for distinguishing healthy controls from patients at baseline (82%), and pregabalin from placebo (82%), independently provides promise for using MVPA for marker identification in analgesic drug development. Future work should refine these results by exploring feature identification techniques (such as recursive feature elimination) and signal normalization considerations.<sup>41</sup>

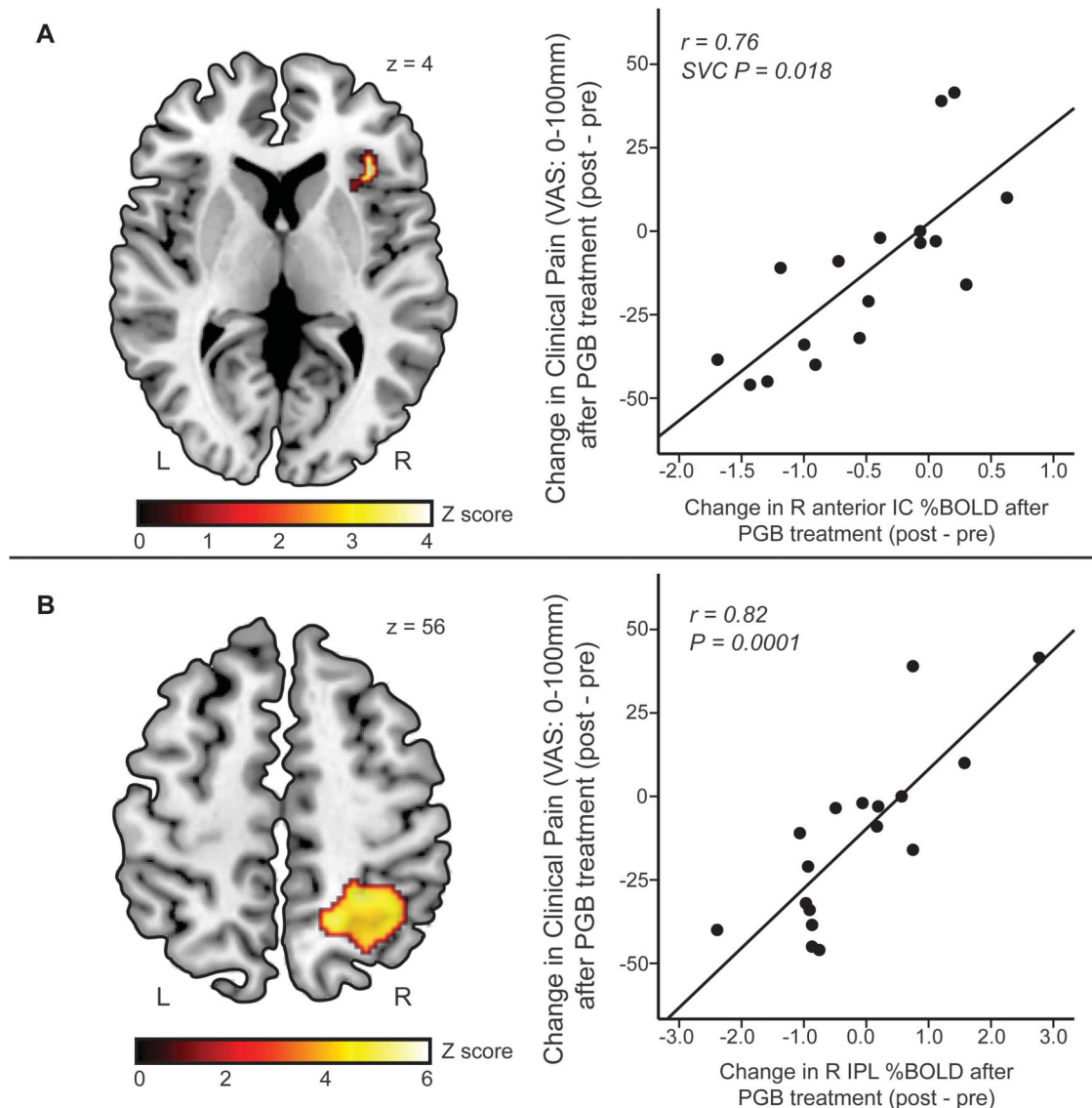
As noted above, our SVM findings have relevance to the development of novel analgesics. Using SVM analysis of the response to visual stimulation, we distinguished pregabalin administration from placebo. By extrapolation, other compounds that target the gain on multisensory integration may also be identified using this simple visual task. Similar methods have been

proposed using various types of painful stimuli.<sup>24</sup> What is interesting here is that our paradigm is easily implemented and may be more specific for patients with pain who suffer from global augmentation of sensory stimuli.<sup>15</sup> We predict that our visual stimulus may differentiate more centrally acting agents from analgesics efficacious in pain of a more peripheral nature, as our visual stimulus bypasses processing by peripheral nociceptors.

It is important to highlight our study's limitations. Our sample consisted of female patients with fibromyalgia, so our conclusions may not generalize to males or those with other chronic pain conditions. In addition, we excluded patients taking commonly prescribed medications for fibromyalgia, further limiting generalizability. During fMRI, we only collected visual stimulus unpleasantness ratings in a small subset of patients, none of whom participated in the pregabalin intervention. These data would have allowed us to directly examine the relationship between insular activation and visual-evoked unpleasantness, as well as pregabalin effects on visual unpleasantness.

Additional studies are required to more fully establish the insula as a common neural substrate underlying augmented responses to somatic pain and other sensory modalities. These should incorporate additional imaging techniques and sensory modalities to evaluate sensory integration and the influence of cross-modal sensory amplification on clinical symptoms. In addition to brightness, we do not know if other parameters, such as frequency, may also contribute to the aversive quality of our visual task. Similarly, future studies should incorporate psychophysical strategies, such as signal detection theory<sup>39</sup> and multiple random staircase<sup>2,32,33,62</sup> procedures, that help mitigate bias effects that can confound sensory assessment. Finally, we did not examine other fibromyalgia clinical factors, including fatigue, poor sleep, and cognitive dysfunction, which may influence sensory processing.

This is the first demonstration that patients with fibromyalgia are hypersensitive to the unpleasantness of experimental visual



**Figure 6.** Association between pregabalin-induced reductions in brain activity and clinical pain in patients with fibromyalgia. Changes in clinical pain (post-pre) as measured using a 100-mm visual analog scale (VAS) were positively correlated with changes in visual stimulus-evoked functional magnetic resonance imaging blood-oxygen-level-dependent (BOLD) responses (post-pre) after pregabalin (PGB) administration. Attenuation of brain activation in the (A) right anterior insular cortex (IC) and (B) right inferior parietal lobule (IPL) by PGB treatment was associated with concomitant reductions in clinical pain.

stimulation and that this sensory augmentation is located in the insula. Moreover, this visual response was associated with experimental and clinical pain, and it was attenuated by pregabalin. Since we were able to use machine learning to determine when patients were taking this compound, this approach might be an effective tool for developing individualized analgesics for this patient population. More generally, we demonstrated that a low-level sensory task can have utility in elucidating underlying chronic pain mechanisms.

#### Conflict of interest statement

S. E. Harte has received research funding from Cerephex, Forest Laboratories, and Merck; and served as a consultant for Pfizer, Analgesic Solutions, Aptinyx, and deCode Genetics. S. E. Harte is also co-inventor of the MAST device used in this study and has the right to receive royalties related to product commercialization. D. J. Clauw has received research funding from Cerephex,

Forest, Merck, and Pfizer and serves as a consultant for Tonix, Theravance, Cerephex, Pfizer, Abbott, Merck, Eli Lilly, UCB, Johnson & Johnson, Forest Laboratories, and Purdue Pharma. D. J. Clauw is a co-inventor of the MAST device used in this study and has the right to receive royalties related to product commercialization. Tobias Schmidt-Wilcke was supported by a grant of the Deutsche Forschungsgemeinschaft, GZ: SchM 2665/11. R. E. Harris consults for and has received grant support from Pfizer. The other authors have no conflicts of interest to declare.

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Author contributions: S. E. Harte and E. Ichesco contributed equally to this work. S. E. Harte, T. S.-Wilcke, D. J. Clauw, and R. E. Harris conceived the project. S. E. Harte, E. Ichesco, S. J. Peltier, and R. E. Harris performed the experiments. S. E. Harte, E. Ichesco, J. P. Hampson, S. J. Peltier, and R. E. Harris analyzed the data. S. E. Harte, E. Ichesco, S. J. Peltier, D. J. Clauw, and R. E. Harris wrote the manuscript. All authors reviewed the data and the final manuscript.

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