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Identification of group differences in predictive anticipatory biasing of pain during uncertainty: preparing for the worst but hoping for the best

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Abstract

Pain anticipation during conditions of uncertainty can unveil intrinsic biases, and understanding these biases can guide pain treatment interventions. This study used machine learning and functional magnetic resonance imaging to predict anticipatory responses in a pain anticipation experiment. One hundred forty-seven participants that included healthy controls (n = 57) and individuals with current and/or past mental health diagnosis (n = 90) received cues indicating upcoming pain stimuli: 2 cues predicted high and low temperatures, while a third cue introduced uncertainty. Accurate differentiation of neural patterns associated with specific anticipatory conditions was observed, involving activation in the anterior short gyrus of the insula and the nucleus accumbens. Three distinct response profiles emerged: subjects with a negative bias towards high pain anticipation, those with a positive bias towards low pain anticipation, and individuals whose predictions during uncertainty were unbiased. These profiles remained stable over one year, were consistent across diagnosed psychopathologies, and correlated with cognitive coping styles and underlying insula anatomy. The findings suggest that individualized and stable pain anticipation occurs in uncertain conditions.

Keywords: Expectation, Insula, Nucleus accumbens, Catastrophizing, Imaging, fMRI, MVPA

1. Introduction

How an individual anticipates an upcoming painful experience modulates how pain is perceived,[49,74,91,94] partly by changing how pain relief mechanisms are engaged.[28,61] Previous studies have shown that by changing an individual's expectation or awareness, the perception of the pain is changed,[43,49,94] and this is reflected through changes in brain activation.[7,12,13,30,34,43,51,59,68,87] Positive expectancy cues (ie, the expectation of analgesia) have been shown to reduce pain and induce placebo analgesia, while negative expectancy cues (ie, expectation of worsening pain) can lead to an increase in reported pain and a nocebo response.[43,44,48–50,62] Anticipation of pain, and of pain relief, is coded in the reward/motivational meso-limbic[57] and interoceptive circuits.[23] Substantial animal literature supports the notion that the activity in the reward/motivation circuit reflects motivated behavior to predict the onset of an aversive event,[36] as well as to seek relief from pain or aversion.[36,96] Likewise, human imaging studies show that activity in the nucleus accumbens (NAc) is associated with both impending pain and pain relief.[6,8,9] Furthermore, the anterior insula is a key part of the brain that participates in expectation of impending pain.[2,3,22,47] It has been shown to mediate negative valence emotions,[14,21,22,26] negative expectation of nocebo hyperalgesia,[32,66,67] increased negative emotional response to experimental pain processing, and anticipation in anxiety/depression and emotional allodynia.[72,73,75,76]

Just as there is individual variability in placebo and nocebo responses,[35] people also differ in their emotional biases. In other words, some individuals are adaptive (those with positive bias), who successfully regulate emotional responses to unpleasant stimuli,[72,78] while others are maladaptive (those with negative bias), who show heightened reactivity, behavioral and cognitive avoidance, helplessness, and increased threat attention.[37–39,53,65,75] This is most important clinically in cases when cues are ambiguous and do not clearly predict an outcome. Although several studies have examined how biasing anticipations leads to biased perceptions and the underlying neuro-circuitries of such biases,[51,87] less is known about the neural bases of individual variability in such anticipatory biases, especially when the outcome is uncertain.

To address current gaps in the field, this study aims to assess the extent to which an individuals' neural activity patterns during acute pain anticipation could identify their positive or negative anticipatory response biases in ambiguous and uncertain

situations. Using machine learning techniques and single-subject data analytics, our primary aims were to create a subject-specific activation pattern distinguishing 2 levels of cued pain anticipation (ie, anticipating a "high" pain stimulus vs anticipating a "low" pain stimulus) and to use this activation pattern to predict the individual's anticipation response patterns during uncertainty. Our secondary aim was to discover subgroups in terms of affective biasing during uncertain conditions and determine whether these related to psychopathology, demographics, pain cognitions, and/or brain structure. Intrigued by a notable overlap in altered pain and anticipatory processes across multiple mental health diagnoses,[5,72,75–77,80] we used a mixed psychopathology chronic pain-free sample for this work. Based on the extensive literature, we hypothesized that both anterior insula and ventral striatum would play an important role in predicting anticipatory biases.

2. Methods

2.1. Participants

Data for 147 subjects (50 female participants, mean ± SD age, 28 ± 6.8 years) were used for this study and combined previously published datasets.[72,73,77,78] Data analyzed and reported here are original, that is, they were not reported in previous publications. The sample described here includes 57 (22 female participants) healthy controls with no current or history of pain, mental illness, or trauma and 90 (28 female participants) subjects in a "mixed psychiatric" group (major depressive disorder N = 35; combat trauma N = 25; mild TBI N = 19; and recovered anorexia nervosa N = 11, all without chronic pain, see **Table 1** for details). Subjects were recruited using flyers at the University of California San Diego (UCSD) clinics, internet sites (eg, Craigslist), local papers, and word of mouth from 2008 to 2011. The study was approved by the UCSD Human Research Protection Program and Veterans Affairs San Diego Healthcare System Research and Development Committee. All methods were performed in accordance with the relevant guidelines and regulations. Before participating, all subjects gave their written informed consent and underwent a Structured Clinical Interview for DSM-IV (SCID)[31] to establish current and past psychiatric diagnoses. All subjects completed behavioral questionnaires, including the Beck Depression Inventory (BDI)–2[10] for depressive symptom severity, the Spielberger State-Trait Anxiety Inventory (STAI-T)[69] for trait anxiety, the Pain Catastrophizing Scale (PCS)[81] for pain coping cognitions, and the Toronto Alexithymia Scale (TAS20)[83] for the ability to identify and evaluate feelings (see **Table 1** for details). Subjects were excluded from the study if they: (1) used psychotropic medication within the last 30 days; (2) fulfilled DSM-IV criteria for alcohol/substance abuse or dependence within 30 days of study participation; (3) fulfilled DSM-IV criteria for lifetime bipolar or psychotic disorder; (4) have ever experienced a head injury with a loss of consciousness of >30 minutes; (5) had clinically significant comorbid medical conditions, such as cardiovascular and/or neurological abnormality, including chronic pain; (6) had irremovable ferromagnetic material; (7) were pregnant or claustrophobic; and (8) were left-handed. All female subjects were scanned during the first 10 days of their menstrual cycle. A subset of these subjects (N = 32) underwent the same pain anticipation paradigm on at least 2 separate occasions. Each scan was roughly 12 months (±1 month) apart. This cohort will be referred to as the replication cohort (see **Table 1** for details).

2.2. Neuroimaging protocol

Two functional magnetic resonance imaging (fMRI) runs (412 brain volumes per run) sensitive to blood oxygen level–dependent (BOLD) contrast were collected for each subject using a 3.0T GE Signa EXCITE scanner (GE Healthcare, Milwaukee, WI) (T2*-weighted echo planar imaging, TR = 1500 ms, TE = 30 ms, flip angle = 90, FOV = 23 cm, 64 × 64 matrix, 30 2.6-mm 1.4-mm gap axial slices) while they performed the pain anticipation paradigm described further. These parameters were optimized for mesolimbic acquisition.[55,64,70] Acquisitions were time-locked to the onset of the task. During the same experimental run, a high-resolution T1-weighted image (FSPGR, TR = 8 ms, TE=3 ms, TI = 450 ms, flip angle = 12, FOV = 25 cm, 172 sagittal slices, 256 × 256 matrix, 1 × 0.97 × 0.97 mm³ voxels) was obtained for anatomical reference. The fMRI protocol was the same for most (N = 125) of the subjects, but a small subset of subjects (N = 22) were scanned separately with a TR of 2000 ms for the T2*-weighted echo planar imaging.

2.3. Pain anticipation functional magnetic resonance imaging paradigm

The pain anticipation paradigm used 2 predetermined and consistent temperatures, 45.5°C and 47.5°C, across subjects to elicit a low-pain (LP) and a high-pain (HP) sensation, respectively. Average postscan subjective ratings were 4.3 ± 2.8 and 1.6 ± 1.7 for HP and LP, respectively. Stimulation was delivered through a 9-cm² thermode (Medoc TSA-II, Ramat-Yishai, Israel) on the participant's left forearm, as described elsewhere.[72] Each trial began with a period of anticipation (10 seconds) initiated by a visual cue (**Fig. 1A**). The cue was always followed by painful stimulation (7 seconds, either HP or LP) and a period of rest (jittered between 24 and 30 seconds) before the next trial began. The schedule of stimuli differed between runs in a pseudorandom and counterbalanced order. A single imaging session included 7 HP trials (HP cue followed by HP stimulation), 7 LP trials (LP cue followed by LP stimulation), and 14 uncertain (UN) trials (nonspecific pain cue followed by either HP or LP stimulation at 50% probability, unknown to the subject). For a more detailed explanation of the pain anticipation paradigm, see supplemental digital content 1, http://links.lww.com/PAIN/C20.

2.4. Functional magnetic resonance imaging image processing

All fMRI data were preprocessed using a MatLab-based functional connectivity toolbox, CONN,[93] to denoise and align the images for analysis (**Fig. 1B**). A detailed account of the preprocessing pipeline is given in supplemental digital content 2, http://links.lww.com/PAIN/C20. Further analysis was conducted using the Analysis of Functional NeuroImages (AFNI) software package.[18] A multiple regression model corrected for autocorrelation consisting of 28 anticipation-related regressors and 28 stimulus-related regressors was applied to preprocessed time series data for each individual, as recommended.[56] A separate regressor was calculated for each trial such that each event had its own estimated amplitude. The 28 anticipation-related regressors modeling the entire anticipation period consisted of: (1) anticipation of moderately painful heat stimulation (HP anticipation), (2) anticipation of mildly painful heat stimulation (LP anticipation), and (3) anticipation of uncertain painful heat stimulation (UN anticipation). All stimulation conditions (HP and LP) were modeled as regressors of no interest. Six additional

Table 1

Sample characteristics.

Full cohort	Healthy controls, n = 57	Mixed psychiatric, n = 90	Stats	
	Mean ± SD	Mean ± SD	t/χ2	P
Demographic variables				
Gender	35 M/22 F	62 M/28 F	0.87	0.35
Age (y)	27.3 ± 7.4	28.4 ± 6.4	0.97	0.33
Race			0.64	0.88
African American	N = 4	N = 5		
Asian	N = 7	N = 8		
Caucasian	N = 30	N = 49		
Other	N = 16	N = 28		
Clinical variables				
Major depressive disorder		N = 35		
Combat trauma		N = 25		
Mild TBI		N = 19		
Recovered anorexia nervosa		N = 11		
BDI-2	3.2 ± 5.7	17.2 ± 12.4	8.0	<0.001
PCS	9.6 ± 9.6	16.5 ± 12.1	3.6	<0.001
TAS-20	39.5 ± 11.6	54.2 ± 13.9	6.6	<0.001
STAI-T	30.2 ± 9.5	47.7 ± 13.2	8.6	<0.001
Replication cohort*	**8 healthy controls**	**24 mixed psychiatric**	**Stats**	
Demographic variables	**Mean**	**Mean**	t/χ2	P
Gender	8 M/0 F	17 M/7 F	1.16	0.28
Age, y	27.1 ± 4.14	26.9 ± 7.2	−0.07	0.94
Race			1.08	0.78
African American	N = 4	N = 13		
Asian	N = 2	N = 9		
Caucasian	N = 1	N = 2		
Other	N = 1	N = 0		

* Replication cohort, 32 subjects from the original full cohort who completed a follow-up session at ~12 mo.
BDI, -2 Beck depression inventory; PCS, Pain catastrophizing scale; STAI-T, Spielberger state-trait anxiety inventory; TAS-20, Toronto Alexithymia scale; TBI, Traumatic brain injury.

regressors were included in the model as nuisance regressors: 1 outlier regressor to account for physiological and scanner noise (ie, the ratio of brain voxels outside of 2 standard deviations of the mean at each acquisition), 3 movement regressors to account for residual motion (in the roll, pitch, and yaw directions) and regressors for baseline and linear trends to account for signal drifts. To reduce the false positives induced by collinearity, time series data were fit using the AFNI[18] program 3dLSS.[56] 3dLSS applies a least squares sum model estimation to the resulting individually modulated time series data to deconvolve BOLD activation in the Multi-Variate Pattern Analysis (MVPA) of task-based fMRI data.[56] This approach was chosen following previous findings that 3dLSS, as opposed to a traditional least squares approaches, achieved higher classification accuracy with low variance[56] (see **Fig. 1B** for the Study Imaging Pipeline).

2.5. Structural analysis

A fully automated processing pipeline, Advanced Normalization Tools (ANTs), was applied to each T1w scan. Preprocessing involved correction of magnetic field intensity in homogeneity (eg, N4 bias correction),[88] extraction of brain tissues, and Atropos n-tissue segmentation.[4] The T1w MRI volume of each subject was spatially normalized to a widely used T1w MRI template in stereotaxic space, the Montreal Neurological Institute/International Consortium for Brain Mapping (MNI-152). Spatial normalization and ROI segmentation results for each scan were inspected visually for accuracy. Morphometric measures including total gray matter volume in mm^3 were estimated using

ANT built-in functions for each ROI (see below). The relative intracranial volume (ICV)–to-template size was determined by calculating the determinant of the affine registration matrix from the ANT registration. The relative ICV value was then multiplied by the ICV of the MNI-152 template to calculate a total ICV value per subject).

2.6. Regional activation maps

Activation maps were created on a single-subject basis. Masks of selected ROIs were created in MNI space using AFNI and Hammers atlas.[27,40] A total of 26 ROIs were chosen based on their prominent roles in pain prediction, processing, and relief.[20,23,30] Twelve ROIs (6 on each side) were selected within the insula[27]: (1) posterior long gyrus, (2) anterior short gyrus, (3) middle short gyrus, (4) posterior short gyrus, (5) anterior inferior cortex, and (6) anterior long gyrus (**Fig. 1B**) based on the prominent role of insular subregions in various aspects of pain prediction and experience[22,34] and the critical role of insula subregions in our prior work on pain anticipation.[72,73] In addition, these ROIs were augmented by 14 functionally relevant bilateral ROIs (7 on each side): (1) anterior cingulate cortex, (2) amygdala, (3) nucleus accumbens, (4) caudate nucleus, (5) putamen, (6) pallidum, and (7) substantia nigra. The anterior cingulate and amygdala ROIs were chosen for their role in affective processing networks, the nucleus accumbens as a vital region of the ventral striatum involved in evaluation, along with its common targets, the pallidum and substantia nigra, and lastly, the caudate nucleus and putamen as representative of the dorsal striatum (see
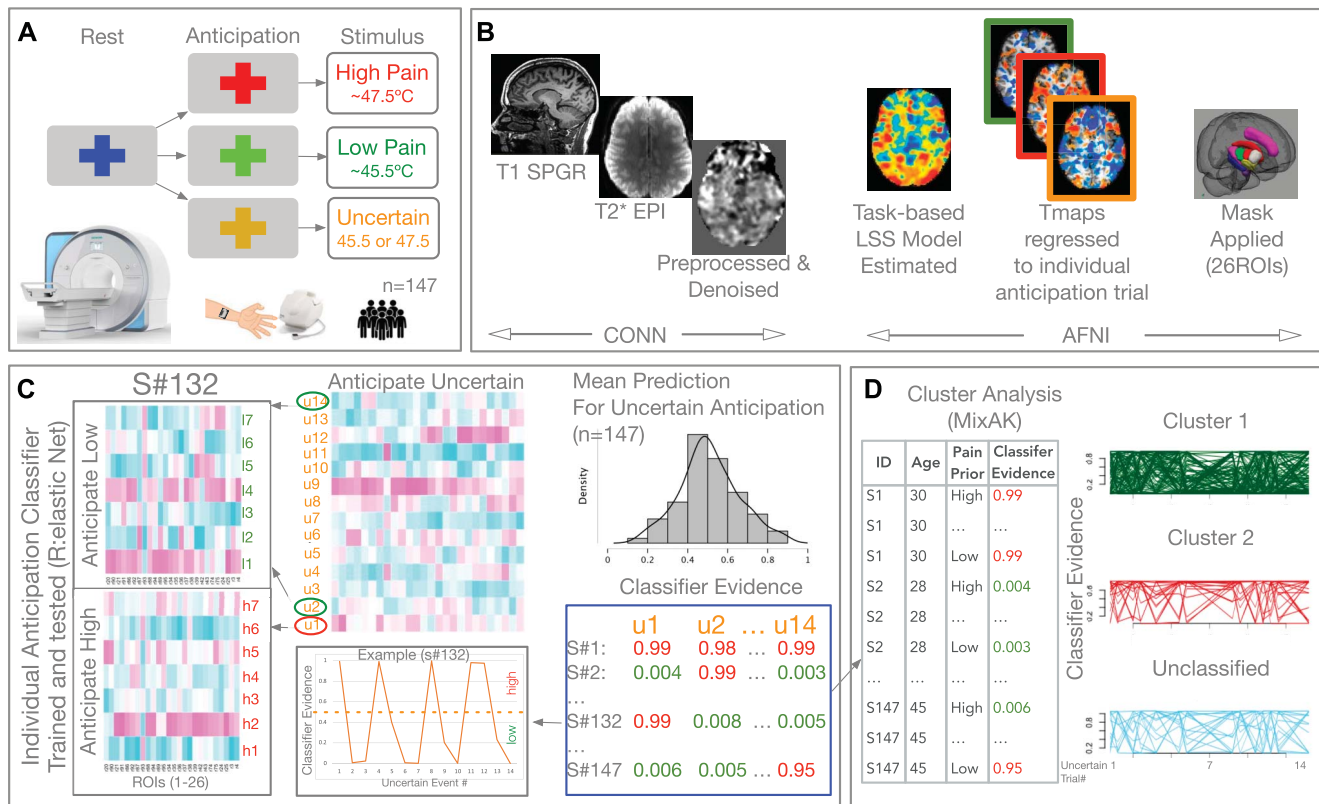
Figure 1. Illustration of applied methods. (A) Data collection: pain anticipation paradigm; high pain (red, N = 7), low pain (green, N = 7), and uncertain pain (yellow, N = 14) visual cues, followed by pain stimulation. (B) Model verification: fMRI preprocessing with CONN toolbox (www.nitrc.org/projects/conn, RRID: SCR_009550) and task-based regression (including least squares sum model) completed in AFNI. Activation maps extracted in 26 a priori–chosen ROIs depicted in glass brain on the right side only for each high and low pain anticipation event (see supplemental digital content 3, http://links.lww.com/PAIN/C20 for further details). Elastic net regression is used to train and test classifier to separate low and high pain anticipation neural patterns (c.f. Methods for more details) (C) Uncertainty prediction: Each uncertain anticipation trial is compared with the certain activation maps and a probabilistic prediction is determined by LASSO. Predictions ≥0.5 are classified as "high," and predictions <0.5 as "low." (D) Group classification: Predictions across all 14 uncertain trials for each subject are provided to mixAK cluster analysis in R, and each subject is clustered based on individual anticipation profile.

supplemental digital content 3, http://links.lww.com/PAIN/C20 for details). Using the AFNI program 3dROIstats,[18] the mean activation was extracted as the beta coefficient from each region during each individual anticipation trial. The use of t values, as opposed to beta coefficients, suppresses the contribution of noisy voxels and has shown improved classification accuracy in previous studies.[54]

2.7. Whole-brain activation maps

To evaluate the significance of effect of anticipation of high pain, low pain, and the difference in the whole sample, the whole-brain linear mixed-effects model (ie, high, low) was run on activation in the HP anticipation and LP anticipation with subject entered as a random factor using AFNI function 3dLMEr.[16] Voxel-level results were thresholded at $P = 0.00005$ and cluster volume of 100 ($P < 0.00005$).[19]

Likewise, to evaluate the significance of effect of heat pain after known and unknown cues for each anticipation bias cluster defined further (ie, positive/unbiased/negative), whole-brain linear mixed-effects model for group (ie, positive/unbiased/negative), and cue (ie, known/unknown) and subject as a random factor was run using AFNI function 3dLMEr.[16] The effects were examined for group activation during each cue, voxel thresholded at $P = 0.00005$ and cluster volume of 300 ($P < 0.00000$). In an exploratory analysis, we also performed a 3dLMEr on the group by cue interaction, voxel thresholded at $P < 0.01$ and a cluster volume of 100.

2.8. Functional analysis of regional activation maps for multi-variate pattern analysis

The average activation within each region underwent regression analysis by way of elastic net. The regression model was executed in R[84] using the *glmnet* package[84] for Lasso and Elastic Net Regularized General Linear Models. Penalized regression methods are especially important in this case because they allow for a smaller number of predictors to be included in the model. In *glmnet*, 2 variables, alpha and lambda, must be specified to control the fit and regularization of the regression model. Alpha represents the elastic net mixing parameter such that a value of 0 uses a ridge penalty, 1 uses a LASSO penalty, and an intermediate value uses a weighted combination of the 2. Lambda is the regularization parameter. Elastic net was performed on a single-subject basis in which the training set was individuals' neural activation (from 26 ROIs simultaneously as independent predictors) during 14 certain anticipation trials (HP and LP as dependent outcome). For the initial training, that is, low pain vs high pain anticipation model, data were split into 2/3 and 1/3 for the training and test sets, respectively. The model was cross-validated (n = 100) using 3 folds on certain anticipation trials, and lambda and then alpha were selected for optimal fit for this training set. The optimal value of alpha for each subject was determined by testing values (0-1) at regular intervals of 0.1 and selecting that which resulted in the greatest subject-specific classification accuracy (see supplemental digital content 4, http://links.lww.com/PAIN/C20). This allowed for accurate and consistent discrimination between

single-subject neurobiological patterns of low pain and high pain anticipation. The optimal model for certain trial separation (ie, HP vs LP) was then applied to predict classification (ie, HP or LP) in the 14 uncertain trials.

2.9. Cluster analysis

Cluster analysis was completed using the R-based package MixAK.[45,46] MixAK uses a generalized linear mixed model (GLMM) with Markov Chain Monte Carlo (MCMC) methods[45,46] to cluster subjects based on the multidimensional (ie, N = 14 uncertain trials separately) probabilistic predictions made for each UN trial obtained from the elastic net model. Effects accounted for in the GLMM included the fixed effect of time and the random effect of the previous pain stimulation experienced (HP or LP). Previous pain was included as a random effect based on findings indicating that prior experiences can modulate the experience of painful stimulation.[7,12,13,34,49,59,94] The model used a normal mixture distribution of random effects. To validate this model, a k-means (k = 3) clustering was also applied that did not include the temporal lagged effect that was provided by the GLMM-MCMC model (X-squared = 150.2, df = 4, $P < 0.001$; Jaccard index = 0.7619).

2.10. Functional analysis of replication cohort

For the subset (N = 32) of the cohort that underwent multiple scanning sessions (**Table 1**), prediction analysis was trained on certain anticipation activation maps from session 1 for each subject and applied to certain anticipation activation maps for the subsequent session.

2.11. Statistical analysis

To explore whether psychiatric and demographic variables influenced predictions, we performed chi-square tests on the elastic net regression analysis results to compare predictions between the healthy controls and mixed psychiatric group, as well as male and female individuals. Pearson correlation tests were performed to assess possible relationships between cluster classification and demographic variables (sex and age). To assess the role of psychological variables (BDI2, PCS, TAS20, and STAI-T) in our predictions of cluster group assignment, logistic regression was performed. Categorical variables were assessed with chi-square tests, 2-tailed t tests, and an ANOVA.

3. Results

3.1. Subject-specific neural response patterns distinguish low pain and high pain anticipation

The study flow is summarized in **Figure 1A–D**. The performance of individualized neural patterns in separating anticipation of high pain vs anticipation of low pain was 97.4 ± 7.9% accurate with 98.4 ± 5.9% sensitivity, 96.5 ± 13.1% specificity, and 97.4% area under the curve (AUC) across all subjects, as indicated by the receiver operating characteristic (ROC) curves in **Figure 2A**. High-pain and low-pain anticipatory neural patterns were separable in 145 of 147 subjects in our study based on a single-subject accuracy threshold of 75% or greater. To ensure that single-subject (or "idiographic") approach to distinguish between the high-pain and low-pain anticipatory neural patterns was the most effective, a group-based (or "nomothetic") approach, based on population-wise activation maps averaged across all subjects,[92] was also performed. This

model assessed the extent to which population-based average pain anticipatory neural patterns distinguished low-pain and high-pain anticipatory neural patterns on the single-subject level. Population-based model performance was 59.4 ± 13.5% accurate across all subjects, with similarly low specificity, sensitivity, and AUC. In addition, only in 22 (15%) subjects, high-pain and low-pain anticipatory neural patterns were separable at a 75% accuracy level using the population-based elastic net model. Whole-brain activation for high pain and low pain anticipation in the entire sample (see Methods), as well as postscanner subjective anticipatory ratings (t[141] = 12.143, $P < 0.001$, ES = 1.022), showed the expected significant differences (**Fig. 2A**, see supplemental digital content 5, http://links.lww.com/PAIN/C20 for detailed activation tables). Across all subjects' elastic net models, insular regions were the most frequently included regional neural activity predictors of low pain vs high pain anticipation neural pattern separation (96% of the subjects), with the anterior short gyrus being the most frequent (63%). Other highly contributing regions were the nucleus accumbens (64%), substantia nigra (61%), and amygdala (60%) (**Fig. 2B**, see supplemental digital content 6, http://links.lww.com/PAIN/C20).

3.2. Subject-specific activation pattern classifies anticipation response patterns during uncertainty

Once we confirmed that neural patterns of low pain and high pain anticipation are separable with high accuracy on an individual level (see above and **Fig. 2A**), we classified each neural pattern during uncertainty into either high pain or low pain anticipation for each individual subject. Classifier decisions at each of the 14 anticipation periods during uncertainty were based on a continuous classifier evidence value (0-1) in that predictions ≥0.5 are classified as "high," and predictions <0.5 as "low." Individual predictions for each uncertain anticipation for a single example subject and average predictions during uncertainty for the entire sample are shown in **Figure 1C**. Of importance, we assessed the stability of each subject's decoded anticipation biases during uncertainty over time. This was examined in a replication cohort of 32 subjects who had repeated fMRI data collection 12 ± 1 months apart (**Table 1**, see supplemental digital content 7, http://links.lww.com/PAIN/C20). Each subject's individualized elastic net modeling of certain anticipatory trials from the first imaging session (train) was applied to uncertain pain anticipation trials of the subject's subsequent imaging session (test). The interclass correlations were highly significant (ICC = 0.72; F [31,32] = 3.6, b = 0.57 [0.44-0.87], $P = 0.00027$), confirming the stability of our predictions during uncertainty.

3.3. Discovery of affective biasing subgroups during uncertainty

3.3.1. Subject cluster by anticipation biases during uncertainty

Our secondary aim was to discover subgroups within anticipatory biases during uncertainty and how factors such as demographics and/or psychopathology may influence subgrouping (**Fig. 1D**). The GLMM identified 3 clusters based on subjects' response patterns to uncertain trials (**Fig. 3A**). The first cluster (n = 55; olive) was characterized by a low-pain anticipatory response to uncertain trials (ie, "positive bias"), the second cluster (n = 47; pink) was characterized by a high pain
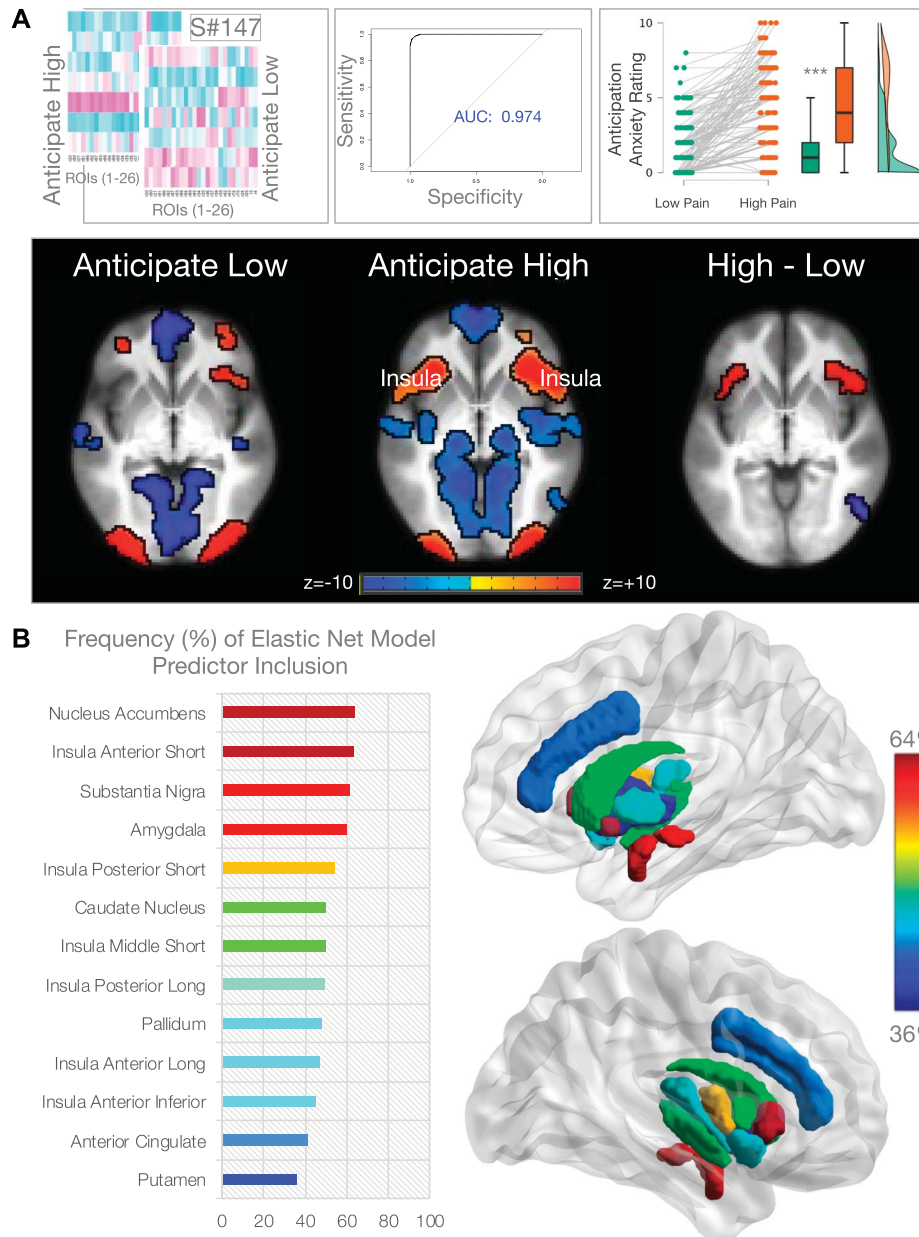
Figure 2. (A) Individual patterns for anticipation high and low pain are shown (representative subject #147). Using an elastic net approach, which allows for optimal selection ranging from penalized regression analysis with least absolute shrinkage and selection operator (LASSO)[86] regularization to ridge regression,[41] the performance of individualized neural patterns in separating anticipation of high pain vs anticipation of low pain was 97.4 ± 7.9% accurate with 98.4 ± 5.9% sensitivity, 96.5 ± 13.1% specificity, and 97.4% area under the curve (AUC) across all subjects. Likewise, subjective ratings for anticipation of high pain and low pain (shown by the raincloud plots) were significantly different (stats). Anticipation-related brain response also significantly differed in the entire sample. (B) Frequency map of regions of interest included in single-subject elastic net models. Models varied between subjects, resulting in a high variation of predictors included in each model. X-axis is frequency (in percent) of inclusion in all single-subject models (N = 147). Brain regions are displayed accordingly.

anticipatory response to uncertain trials (ie, "negative bias"), and the third cluster (n = 45; dark grey) was not a strong fit to the first or second clusters (ie, "unbiased") and had ~0.5 average likelihood across all uncertain trials. As expected, there was a statistically significant difference between the subgroups in their average probability during uncertainty (F[2,144] = 225, P < 0.0001). Furthermore, as demonstrated in **Figure 3B**, regardless of previous pain stimulation, "Positive Bias" cluster subjects (olive) were more likely to anticipate low pain (yellow), and "Negative Bias" cluster subjects (pink) were more likely to anticipate high pain (orange). The unclassified subjects "un-biased" (dark grey) anticipated low pain and high pain at

approximately 50% after high pain, while after low pain, the unbiased group anticipated high pain more often than low pain (χ2 =4.555, P = 0.0328). The three-cluster solution was robust and consistent with the k-means model (see Methods and see supplemental digital content 8, http://links.lww.com/PAIN/C20). We further examined whether anticipation bias groups differed in the feature importance that provided pattern separation in high and low anticipation conditions (**Fig. 2C**). Specifically, we examined subject-level importance scores and determined whether weights differed by ROI, the affective bias cluster group, and their interaction. We found that the importance scores of these ROIs were significantly different (ANOVA, F[12,1236]=
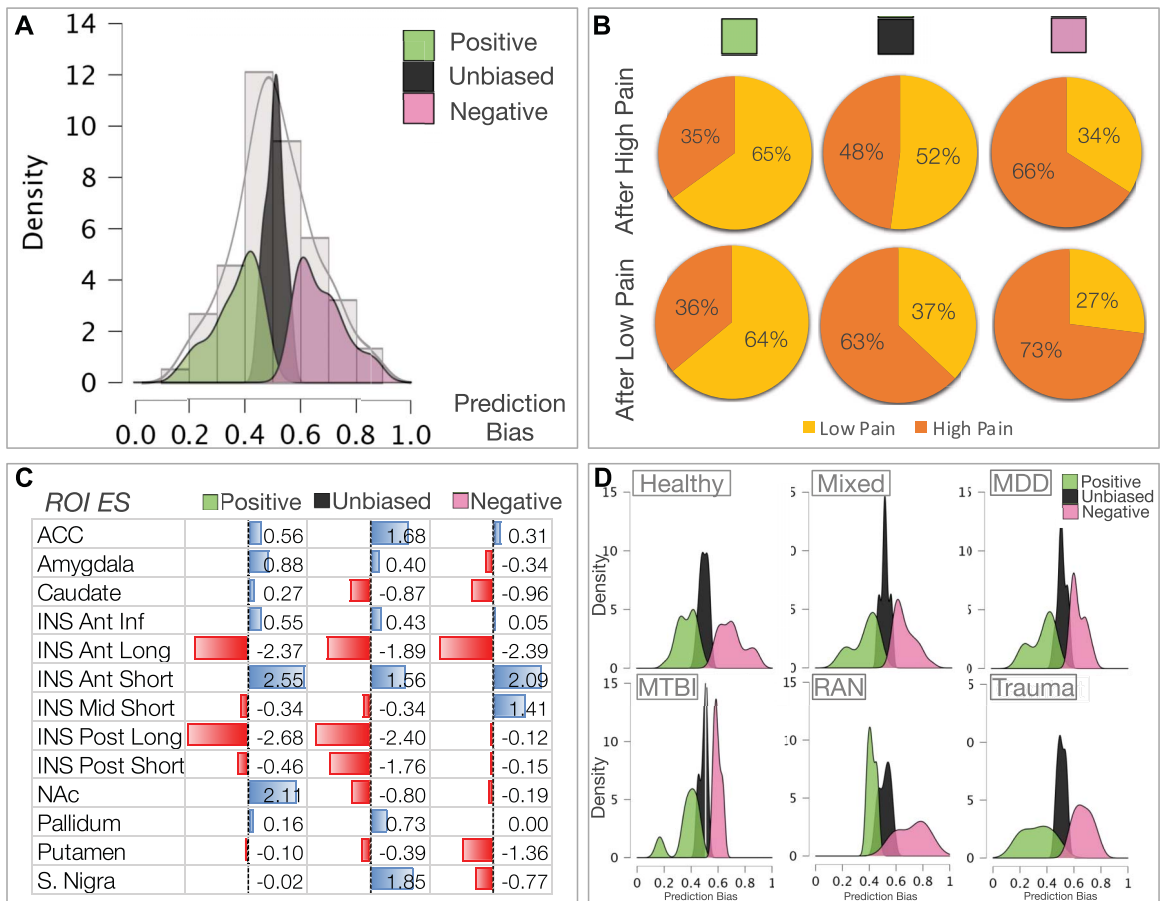
Figure 3. (A) Distribution of anticipatory bias across affective biasing groups: Histograms depicting cluster classification versus average predictions. The GLMM model identified, 3 clusters based on subjects' response patterns to uncertain trials. The first cluster (n = 55; olive) were characterized by a low-pain anticipatory response to uncertain trials (ie, "positive bias"), the second cluster (n = 47; pink) were characterized by a high-pain anticipatory response to uncertain trials (ie, "negative bias"), and the third cluster (n = 45; dark grey) were not strong fits to first or second clusters (ie, "unbiased") and had ~0.5 average likelihood across all uncertain trials. As expected, there was a statistically significant difference between the subgroups in their average probability during uncertainty (F[2,144] = 225, $P < 0.0001$). Predictions during uncertain trials for the entire sample are depicted in the histogram. (B) Proportion of affective biasing by pain prior in each cluster: Regardless of previous pain stimulation, "Positive Bias" cluster subjects (olive, left) were more likely to anticipate low pain (yellow), and "Negative Bias" cluster subjects (pink, middle) were more likely to anticipate high pain (orange). The unclassified subjects "Unbiased" (dark grey, right) anticipated low pain and high pain at approximately 50% after high pain, while after low pain, the unbiased group anticipated high pain more often than low pain ($\chi 2 = 4.555$, $P = 0.0328$). (C) Regional feature importance by affective biasing subgroups. Subject-level importance scores in predicting neural separation of high and low pain anticipation were examined to determine whether weights differed by ROI, the affective bias cluster group, and their interaction. The importance scores of these ROIs were significantly different (ANOVA, F[12,1236]= 3.8905, $P = 6.91E-06$), but there was no main effect of group (F[2,1236] = 0.3598, $P = 0.6979$) and no group by ROI interaction (F[24,1236] = 0.8337, $P = 0.6954$). (D) Anticipatory bias cluster classification vs clinical subgroups. Density maps depicting average prediction of subjects' diagnostic group vs cluster classification within the healthy controls, mixed psychiatric group, individuals with major depressive disorder (MDD), those with mild traumatic brain injury (mTBI), women with recovered anorexia nervosa (RAN), and those with mixed combat trauma. There was no significant difference in cluster classification within any of the aforementioned diagnostic groups (P's > 0.005). Mixed combat trauma included veterans with comorbid major depression, posttraumatic stress disorder, and mild TBI.

3.8905, $P < 0.0001$) but that there was no main effect of group (F(2, 1236)= 0.3598, $P = 0.6979$) and no group by ROI interaction (F[24,1236]= 0.8337, $P = 0.6954$) (**Fig. 3C**).

3.3.2 . Classification based on neural activity patterns during uncertainty only weakly relates to mental health diagnosis and demographics

Density maps depicting average prediction of subjects' diagnostic group vs cluster classification are shown in **Figure 3D** separately for the healthy controls and mixed psychiatric, depression (MDD), mild TBI, recovered anorexia nervosa (RAN), and combat trauma group. A formal comparison between anticipatory biases by mental health status was not significant ($\chi^2 = 6.037$; $P = 0.643$). Comparison of "healthy" and the "mixed psychiatric" cohort was also not significant ($\chi2 = 4.017$, $P = 0.134$). Similarly, there were no

significant effects when comparisons were made between "healthy" and individual diagnoses (P's > 0.05). Likewise, biological sex was not a significant predictor of cluster classification ($\chi^2 = 1.026$, $P = 0.599$).

3.3.3 . Classification based on neural activity patterns during uncertainty relates to cognitive coping styles

To validate our findings, we wanted to examine whether brain-based classification of individuals' anticipatory response biases during uncertainty into adaptive ("positive bias") and maladaptive ("negative bias") anticipators is supported by individual's cognitive coping styles and/or emotional factors. To determine whether and what cognitive/emotional factors explain the biologically determined differences between the 2 well-defined and stable neural clusters, ie, "positive bias" cluster (olive, **Fig. 3A**) and "negative bias" cluster (pink, **Fig. 3A**), we performed logistic
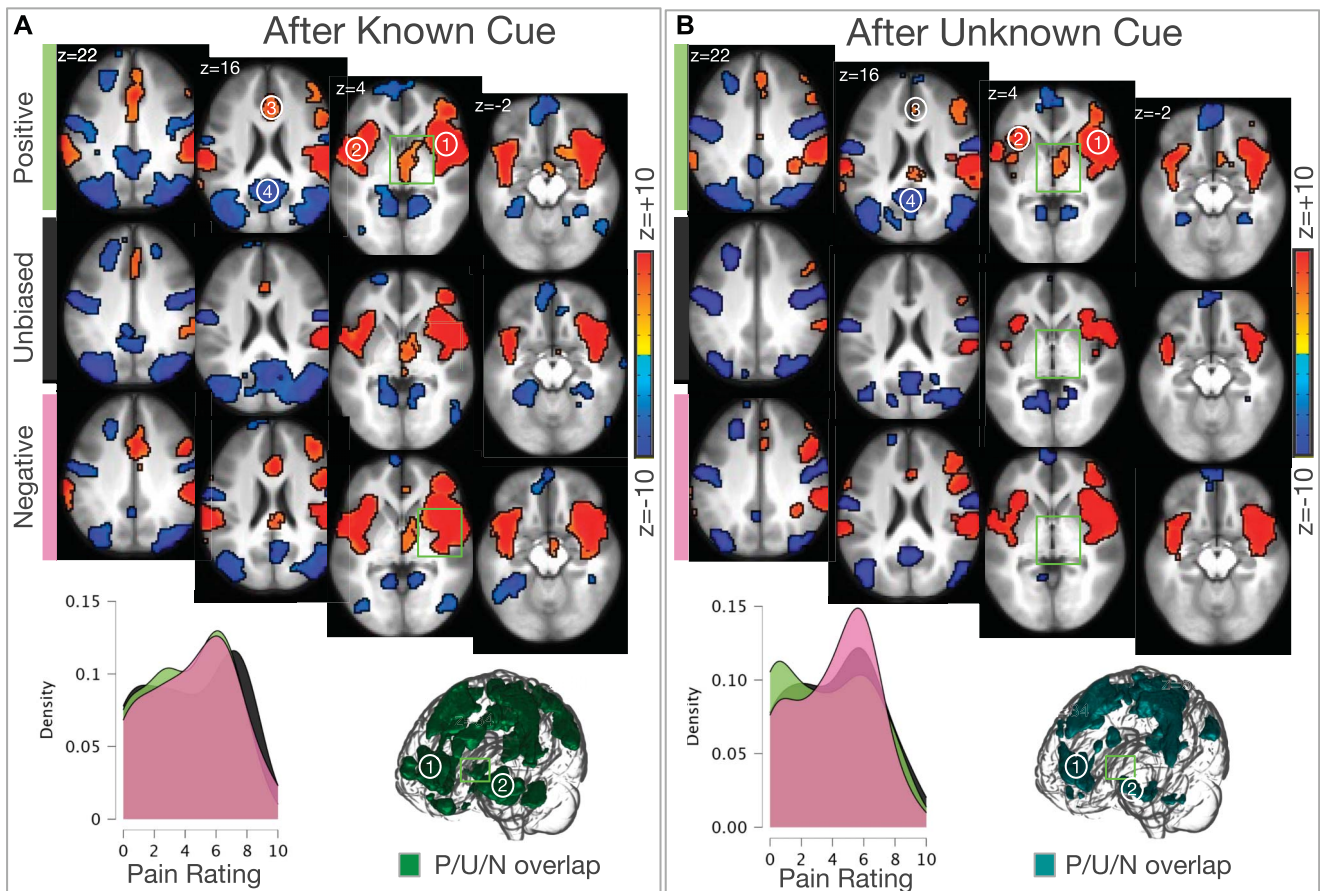
Figure 4. (A) Brain pain maps following known cue: Pain-related brain response in each of the 3 affective bias clusters (positive bias, olive, top row; unbiased, dark grey, middle row; and negative bias, pink, bottom row) during high pain stimulus following known cue, corresponding subjective ratings and overlap between the 3 affective biasing subgroups rendered on a glass brain (dark green). All groups showed overlapping activation within most of the regions (glass brain, dark green overlap map, see supplemental digital content 11, http://links.lww.com/PAIN/C20 for detailed activation tables) including activation of the bilateral insula (1, 2), anterior cingulate (3), striatum (green square), and deactivation within the default mode network regions (4). Subjective pain ratings did not differ significantly in the 3 clusters during high pain stimulus following known cue. (B) Brain pain maps following unknown cue: Pain-related brain response in each of the 3 affective bias clusters (positive bias, olive, top row; unbiased, dark grey, middle row; and negative bias, pink, bottom row) during high pain stimulus following unknown cue, corresponding subjective ratings and overlap between the 3 affective biasing subgroups rendered on a glass brain (teal). All groups showed overlapping activation within most of the regions (glass brain, teal overlap map, see supplemental digital content 11, http://links.lww.com/PAIN/C20 for detailed activation tables) including activation of the insula (1, 2), anterior cingulate (3), and deactivation within the default mode network regions (4). However, only the "positive bias" group (olive, top row) showed striatal activation during pain following the unknown or uncertain cue (green square). Despite segregated densities, subjective pain ratings did not differ significantly in the 3 clusters during high pain stimulus following the unknown cue.

regression with subscales of PCS, TAS20, STAI-T, and BDI-2 used as predictors, while also accounting for age and gender. The results of logistic regression showed that helplessness from PCS (ES = 0.22603; SE = 0.08049, Z = 2.81, P = 0.005), and to a lesser degree difficulty to describe feelings from TAS20 (ES = 0.14402, SE =0.07248, Z = 1.99; P = 0.047), showed significant differences between these 2 clusters, that is, individuals with positive and negative biases. Of importance, helplessness from PCS further differentiated all 3 clusters as determined by k-means clustering (ES = 0.1456; SE = 0.0724; Z = 2.01; P = 0.044) (see supplemental digital content 9, http://links.lww.com/PAIN/C20).

3.3.4. Classification based on neural activity patterns during uncertainty relates to brain structure

To assess to what extent the anatomic architecture was associated with the decoded anticipatory response biases during uncertainty, we estimated gray matter tissue volume of 26 regions of interest (see Methods). Oof these 26 regions, only the volume of the right anterior short insular gyrus was

significantly and inversely associated with the average anticipatory response bias during uncertain trials (Pearson correlation coefficient r = −0.262, P < 0.05, corrected for multiple comparisons, df = 145, see supplemental digital content 10, http://links.lww.com/PAIN/C20), indicating that those with the greatest right anterior short insular gyrus volume were more likely to anticipate low pain during uncertainty (ie, more likely to show a "positive bias").

3.4. Pain-related blood oxygen level–dependent response in affective bias subgroups

The average pain-related whole-brain response (see Methods) and subjective pain ratings in 3 affective bias subgroups and their overlap are shown in **Figure 4A**, following the known cues, and in **Figure 4B**, following the unknown cues. All groups showed overlapping activation within most of the regions (see supplemental digital content 11, http://links.lww.com/PAIN/C20 for detailed activation tables) including activation of the insula and deactivation within the default mode network regions. Notably,
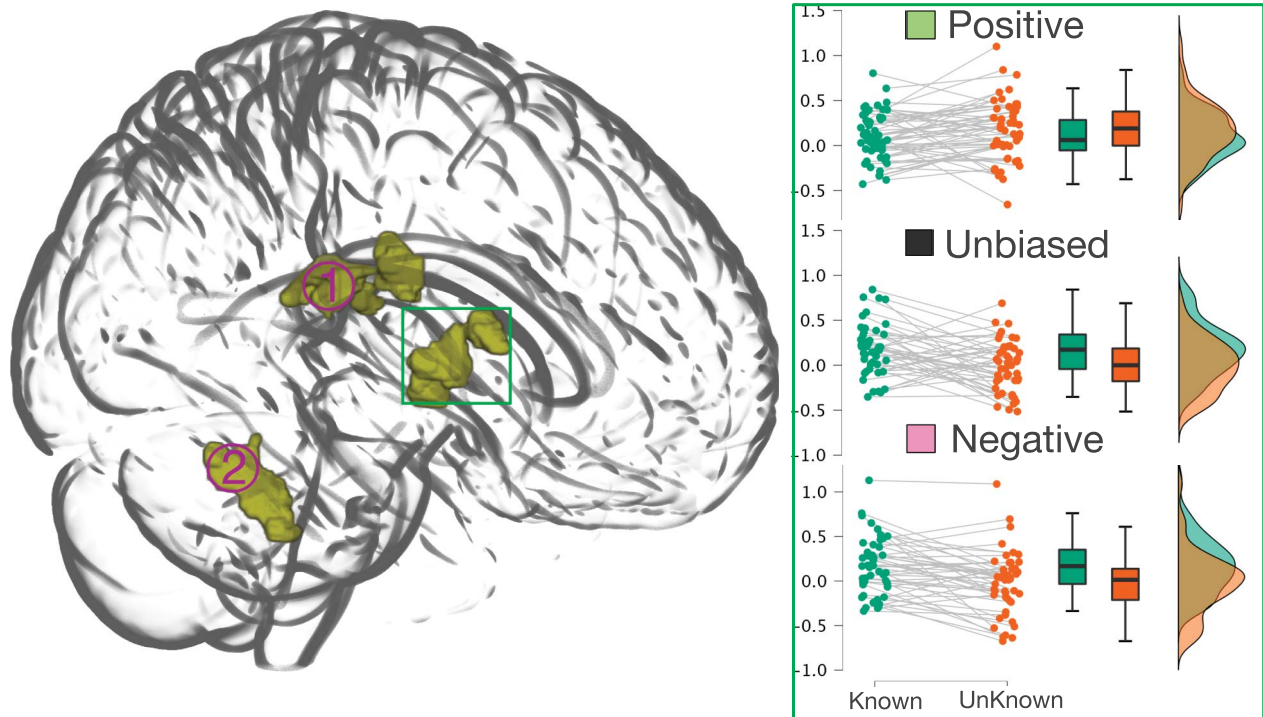
Figure 5. Group-by-Cue Interaction Effects. Exploration of the voxel-wise affective bias group-by-cue interaction effects showed 3 clusters that survived significance at $P < 0.01$ (cluster threshold 100). Clusters were located in the (1) posterior cingulate gyrus (x/y/z: $-2/-27/21$; $\chi2 = 10.4$; 265 voxels, (2) right fusiform gyrus (x/y/z: $42/-32/-21$; $\chi2 = 10.6$; 122 voxels, and the right striatal region (x/y/z: 18/7/9; $\chi2 = 9.3$; 101 voxels, green square). Raincloud plots show that activation within this cluster between known and unknown cues increased in the "positive bias" group only, while in the "negative" and the "unbiased" groups, activation within this cluster between known and unknown cues decreased.

the striatum showed overlapping activation during pain following the known cue (**Fig. 4A**, green square). However, only the "positive bias" group (olive) showed striatal activation during pain following the unknown or uncertain cue (**Fig. 4B**, green square). Exploration of the voxel-wise group by cue interaction effects identified 3 clusters that survived significance at $P < 0.01$ (cluster threshold 100) (**Fig. 5**). Clusters were located in the posterior cingulate gyrus (x/y/z: $-2/-27/21$; $X^2 = 10.4$; 265 voxels), right fusiform gyrus (x/y/z: $42/-32/-21$; $X^2 = 10.6$; 122 voxels), and the right striatal region (x/y/z: 18/7/9; $X^2 = 9.3$; 101 voxels). Exploration of the interaction effects confirmed that the striatal cluster was activated during pain following both, the known and unknown cues in the "positive bias" group only (**Fig. 5**). Likewise, subjective pain ratings showed variability following the unknown cue that matched the positive/negative bias subgrouping, that is, lower in the "positive bias" group following the unknown cue (**Fig. 4B**). However, the affective biasing group (positive, negative, and unbiased) by cue (known, unknown) interaction was not significant (F[1,2,111] = 1.321, $P = 0.271$).

4. Discussion

The goal of this study was to assess the extent to which an individuals' neural activity patterns during cued anticipation of high and low painful stimulus could identify their positive or negative anticipatory response biases during ambiguous or uncertain situations. Our major findings are as follows. First, using a multivariate pattern analysis and single-subject analytics, it is possible to distinguish between subjects' neural activation patterns of anticipation of high and low pain stimuli with high accuracy, sensitivity, and specificity. Second, nucleus accumbens and dorsal anterior insula were the 2 brain regions that

contributed most frequently to the distinction between the neural patterns of high and low pain anticipation. Third, 3 clusters of subjects were defined from the response patterns to uncertain anticipatory cues: (1) positive bias, (2) negative bias, and (3) unbiased. Fourth, these individual neural response patterns during uncertainty were stable over time and suggested mechanistic differences in brain activation when pain was experienced. Five, we found that the 3 groups clustering solution was related to cognitive coping styles and the underlying anatomical architecture and less to mental health status and demographics. These findings add valuable information to the current models of the expectation of pain and extend current knowledge on perceptual biases to unique neural biases during pain anticipation in uncertainty.

The main and unique finding from this study is that an individual's neural activation patterns show stable biases when anticipating pain during uncertainty. We identified 3 affective biasing subgroups based on anticipatory neural patterns during uncertainty. Using personalized elastic net models on low and high pain anticipation, we categorized uncertain pain anticipation as high or low. Results showed 37% anticipate low pain (positive bias), 32% anticipate high pain (negative bias), and 31% were unbiased. Notably, subgroups differed in anticipatory behaviors toward pain stimulation priors. Positive and negative bias clusters consistently anticipated low or high pain, regardless of prior stimulus. Conversely, prior stimulus influenced unbiased cluster's uncertainty anticipations—equal anticipation after high pain, more high pain anticipation after low pain ($\chi^2 = 4.555$, $P = 0.0328$). This hints that these subjects' predictions might be influenced by prior experiences rather than predetermined.

The premise of most pain as predictive signal models is based on updating information.[33] When sensory evidence fails to

confirm the prediction, either the sensory evidence is ignored and, in turn, biases perception, or the brain learns from the error and updates subsequent predictions and evaluations to keep bias in check.[29,63] Our findings demonstrate that there is variability in an individual's updating processes, that is, some predictions are predetermined and less influenced by sensory inputs. Strikingly, when we examined these predictions in the replication cohort 1 year later, these biases showed significant stability. This suggests that the observed differences in affective biasing during uncertainty had less to do with learning and more to do with the fundamental differences in predictions that could remain stable over time. Of importance, we confirmed that the brain response to pain is in fact more about prediction and less about evaluation.[1,15,30] We found that once the pain was actually experienced, it was evaluated similarly across the 3 affective biasing groups. Nevertheless, the whole brain response to pain differed, albeit at a more lenient exploratory threshold level ($P < 0.01$) matching the affective biasing subgroupings. The most striking observation was striatal activation during pain that followed the unknown cue, which was observed in the positive bias subgroup only. We posit that relief-related processes[8,9,36,96] are recruited more readily during anticipation in the positive bias group; hence, they are more likely to predict low pain even when the situation becomes uncertain. Although the observed interaction must be interpreted with caution, this represents an interesting mechanistic interpretation for positive affective bias behavior and a plausible avenue for future research.

Notably, affective biasing clusters did not consistently correspond to specific DSM-IV–defined mental illnesses. This is not surprising given the intertwined nature of various psychiatric and pain conditions.[5,72,75–77,80] Thus, our results suggest that anticipatory biases during uncertainty are likely to cut across various diagnoses. However, biasing clusters did align with vital transdiagnostic pain behaviors; specifically, the helplessness aspect of pain catastrophizing and, to a lesser degree, difficulty in describing feelings from the Toronto alexithymia scale (TAS20).[42,82] Catastrophizing significantly affects experimental and clinical pain responses[25,58,82,89] and is linked to psychopathology.[58] High catastrophizing associates with chronic pain development, severity, disability, and treatment resistance.[11,24,95] Thus, our findings concur with previous data on catastrophizing and extend these data to include neutral affective biasing clusters.

Several studies have demonstrated a mechanistic role of predictions in influencing pain perception in processes that are believed to occur through modulation of pain-related brain response,[87] such as perceptual biasing by cues.[1,15] Recent work shows that perceptual biasing is consistent with predictive pain models, that is, it can be reduced with increases in prediction error but cannot be fully corrected, even when the prediction error is at its highest.[87] These findings are in direct agreement with the current observations showing that neural predictions are predetermined in approximately 70% of individuals, are stable over time, and are less influenced by sensory inputs. Furthermore, the degree of updating of prediction errors to threat cues is influenced by cognitions.[51] Those with more catastrophic thinking about pain and less mindfulness are significantly more reliant on predictions than on the sensory evidence from the pain stimulus.[51] These behavioral differences map to variability in responses in the striatum, a finding not dissimilar to ours. The finding that higher perceptual bias (rating) towards cues was related to higher pain catastrophizing is also in direct agreement with our findings.

Although the regions of interest (ROIs) chosen for this study were previously implicated in multidimensional pain experience,[39,53,60,72,74,90] we found that the predictive value of each region for low vs high pain anticipation discrimination varied widely across subjects and did not differ between the 3 affective bias groups. The most common regions predictive of low vs high anticipatory responses included the insular regions (particularly the anterior short gyrus) and the nucleus accumbens, with varying inclusion frequencies in the individualized elastic net models. The frequent inclusion of the nucleus accumbens, which has previously been implicated in the anticipation of pain and pain relief,[6] as well as in animal studies of pain-predictive, cue-influenced decision-making,[68] suggests that there is a synergistic relationship between the anticipation of pain and the expectation, or hope, of relief from pain. Likewise, the role of anterior insula in pain processing and anticipation cannot be overstated.[2,3,14,21–23,26,32,47,66,67,72,73,75,76] In fact, we recently showed a brain mechanism associated with chronic neuropathic pain may be acting through increased aversion or emotional distress during expectation of pain relief within this region.[71] Specifically, we observed a significant interaction within the right anterior insula during relief expectation in a chronic pain group when a painful stimulus was at the site of the endogenous pain.[71] Based on our recent work,[79] we believe that the NAc-insula connection provides a balance between pain and pain relief and that functional connectivity between these regions at rest underlies a healthy (or resilient) response to stressful and/or threatening events. Communication between these nodes may assist in building a better predictive estimation of pain/tissue damage.

A limitation of this study is the unequal gender representation, despite the known influence of sex on pain anticipation and perception, with female individuals often experiencing greater psychological distress from pain.[52,85] Although our results did not distinctly differentiate anticipation bias patterns based on sex or psychiatric diagnoses, future research with larger unique diagnostic samples is still warranted. Similarly, while our findings linking helplessness to affective biasing clusters are robust, replication will be needed. In addition, optimism measures and perceptual biases, unexamined in this study, offer avenues for future investigation. Of importance, considering the significance of relief expectation in chronic pain,[17] replicating our findings in a chronic pain sample are imperative. Exploring affective biasing in individuals experience chronic pain could provide important clinical insights and extend these findings into practical cost-effective applications.

5. Conclusions

The stable anticipation bias–derived subject clusters identified here are a corollary of having an optimistic or pessimistic filter. By identifying whether uncertain cues were mapping to low or high pain, the individual's propensity towards optimistic or pessimistic assumptions could be assessed. This neurally derived cue biasing was related to a clinical measure of helplessness, further validating the conceptualization of cue response as important in understanding predicted pain experience. We suggest that these acute automatic predictions in the face of uncertainty are stable overtime and may be critical to catastrophizing. The predictions of pain can influence or determine an individual's experience of pain. Thus, the delineated subject clusters could be indicative of vulnerabilities to pervasive attitudes on threat, and these may respond differently across sex due to either societal or biological interactions. Further study of how this automatic biasing architypes may influence clinical treatment outcomes is

important. While fully mechanistic work of this nature is not imminently available in clinical settings, it is our hope that techniques such as those presented in this study, potentially using more broadly available and requiring lower overhead, can be streamlined and made available to clinics to ascertain objective measurements of intrinsic behaviors and guide pain interventions.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/C20.

Supplemental video content

A video abstract associated with this article can be found on the *PAIN* website.

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