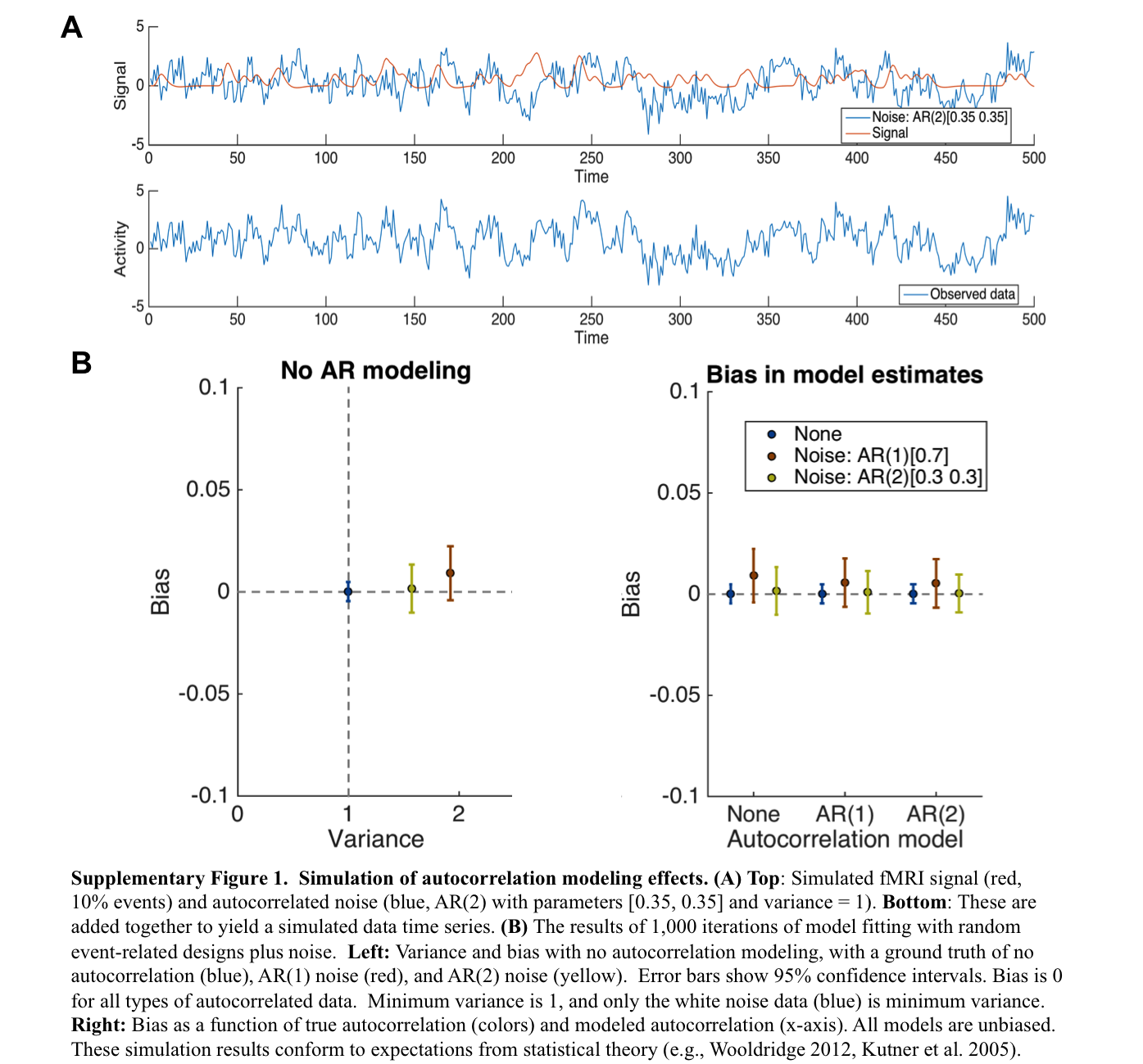
Supplementary Figure 1

  
**Supplementary Figure 1. Simulation of autocorrelation modeling effects. (A) Top**: Simulated fMRI signal (red, 10% events) and autocorrelated noise (blue, AR(2) with parameters [0.35, 0.35] and variance = 1). **Bottom**: These are added together to yield a simulated data time series. **(B)** The results of 1,000 iterations of model fitting with random event-related designs plus noise. **Left:** Variance and bias with no autocorrelation modeling, with a ground truth of no autocorrelation (blue), AR(1) noise (red), and AR(2) noise (yellow). Error bars show 95% confidence intervals. Bias is 0 for all types of autocorrelated data. Minimum variance is 1, and only the white noise data (blue) is minimum variance. **Right:** Bias as a function of true autocorrelation (colors) and modeled autocorrelation (x-axis). All models are unbiased. These simulation results conform to expectations from statistical theory (e.g., ([1](#_ENREF_1), [2](#_ENREF_2))).

Supplementary Figure 2

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**Supplementary Figure 2. A.** Nociception-negative NPS (NPSn) brain map of weights and pattern response values per group and region (ACC, anterior cingulate cortex). Please note that, for simplicity, pattern response magnitudes (Supplementary Figure 2A, bar graphs) are signed such that increases in pattern response indicate increases in pain *activation* in these regions. **B.** Pain-evoked activation (Beta values) for each NPSn region. \*\*\*, p <0.0001; \*\*, p <0.01. \*, p<0.05.

Supplementary Table 1

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Supplementary Table 1.** **NPSp and NPSn pattern response values in response to pressure pain in FM patients and Healthy participants, and between-group differences.** | | | | | | |
| ***NPSp*** | FM Pat. 4kg/cm2 mean (± SD) | Healthy participants 4kg/cm2 mean (± SD) | Healthy participants 6kg/cm2 mean (± SD) | FM vs. Cont. 4kg/cm2 t (p) | FM vs. Cont. 6kg/cm2 t (p) | Cont. 6kg/cm2 vs. Cont. 4kg/cm2 t (p) |
| L Ant. Mid. Insula/Basal G./Operculum | 1.62 (1.1) | 0.91 (0.54) | 1.57 (1.03) | 3.46 (<.001) | 0.20(0.84) | 3.26(0.001) |
| R Ant. Mid. Insula/Basal G./Operculum | 0.42(0.37) | 0.30(0.20) | 0.44 (0.27) | 1.75 (0.08) | -0.20 (0.84) | 2.37(0.02) |
| L Post. Insula/SII | 1.22 (0.71) | 0.67 (0.36) | 1.05 (0.81) | 4.08 (<.001) | 0.91 (0.37) | 2.45 (0.02) |
| R Post. Insula/SII | 0.81 (0.62) | 0.56 (0.38) | 0.94 (0.64) | 2.09 (0.04) | -0.82 (0.41) | 2.95 (.004) |
| dACC/SMA | 1.38 (1.06) | 0.84 (0.97) | 1.33 (0.99) | 2.28 (0.03) | 0.22 (0.83) | 1.98 (0.05) |
| Thalamus/Midbrain | 0.39 (0.37) | 0.25 (0.26) | 0.44 (0.32) | 1.84 (0.07) | -0.53 (0.60) | 2.52 (0.01) |
| Inf. Frontal Gyrus | 0.02 (0.07) | 0.01 (0.03) | 0.03 (0.05) | 0.36 (0.72) | -0.95 (0.35) | 1.88 (0.06) |
| Amygdala | 0.10 (0.12) | 0.04 (0.07) | 0.08 (0.11) | 2.38 (0.02) | 0.58 (0.56) | 1.65 (0.10) |
| ***NPSn*** |  |  |  |  |  |  |
| pgACC | 0.66 (1.31) | 0.03 (0.74) | 0.18 (0.94) | 2.50 (0.01) | 1.65 (0.10) | 0.71 (0.48) |
| precuneus/paracentral lobule | 0.90 (1.01) | 0.27 (0.65) | 0.86 (0.97) | 3.10 (0.002) | 0.15 (0.88) | 2.87 (0.01) |
| NPS, Neurologic Pain Signature; FM Pat., Fibromyalgia Patients; Left; Ant., Anterior; Mid., Middle; Post., Posterior; SII, secondary somatosensory area; dACC, Dorsal Anterior Cingulate Cortex; SMA, Supplementary Motor Area; Inf., Inferior; pgACC, perigenual ACC; PCC, posterior cingulate cortex. | | | | | | |

Supplementary Table 2

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| **Supplementary Table 2. Brain regions most reliably contributing to the FM-pain classification pattern (FDR corrected, 10,000 bootstrap tests)** | | | | |
|  |  | *Cluster size, mm3 (voxels)* | *x y z* | *z* | |
| Regions showing **positive** voxel weights (relatively increased activation) | | | | | |
| Brainstem | | 312 (39) | 8 -18 -46 | 4.24 | |
| R Lingual/ Fusiform Gyrus | | 216 (27) | 28 -50 -6 | 4.23 | |
| L Postcentral gyrus/parietal operc/L insula | | 752 (94) | -58 -14 34 | 4.57 | |
| R postcentral gyrus | | 24 (3) | 62 -14 26 | 3.95 | |
| Dorsomedial PFC | | 144(18) | 0 60 30 | 4.31 | |
| Ventromedial PFC | | 24 (3) | -12 60 8 | 3.85 | |
| Ventrolateral PFC | | 24 (3) | 34 58 -2 | 4.03 | |
| Regions showing **negative** voxel weights (relatively reduced activation) | | | | | |
| R Cerebellum | | 480 (60) | 30 -88 -26 | -4.53 | |
| Parahippocampal Gyrus | | 48 (6) | -24 -26 -20 | -4.03 | |
| Middle/Inf. Temporal Gyrus | | 144 (18) | 58 -16 -20 | -4.34 | |
| R lateral PFC | | 1120 (140) | 44 8 26 | -4.65 | |
| L Superior Parietal | | 24 (3) | -22 -60 42 | -4.01 | |
| x y z are coordinates given in Montreal Neurological Institute (MNI) space. Statistics correspond to a corrected threshold PFDR < 0.05, 10,000 bootstrapping procedure. R, right; L, left. operc. Operculum; PFC, prefrontal cortex. | | | | |

Supplementary Table 3

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| **Supplementary Table 3. Brain regions most reliably contributing to the Multisensory classification pattern (FDR corrected, 10,000 bootstrap tests)** | | | | |
|  |  | *Cluster size, mm3 (voxels)* | *x y z* | *z* | |
| Regions showing **negative** voxel weights (relatively reduced activation) | | | | | |
| Cerebellum R | | 20072 (2509) | 32 -84 -24 | -5.44 | |
| Cerebellum L | | 5648 (706) | -32 -74 -30 | -5.04 | |
| Inferior Occipital Gyrus R and medial | | 16392 (2049) | 8 -98 -8 | -5.98 | |
| Inferior/Middle Occipital Gyrus L | | 10768 (1346) | -22 -104 4 | -5.37 | |
| Superior/Middle Temporal Gyrus R | | 9984 (1248) | 62 -14 -4 | -3.99 | |
| Superior/Middle Temporal Gyrus L | | 10768 (1346) | -70 -28 2 | -5.61 | |
| L Precentral Gyrus | | 2776 (347) | -42 -8 62 | -3.60 | |
| R Middle Frontal Gyrus | | 1168 (146) | 26 -2 46 | -4.13 | |
| L Hippocampus | | 904 (113) | -28 -20 -10 | -4.1 | |
| Midbrain | | 2816 (352) | -6 -20 -8 | -3.77 | |
| R Ventral Striatum/Putamen | | 1664 (208) | 12 6 -4 | -3.56 | |
| L Putamen | | 1272 (159) | -20 2 -2 | -3.85 | |
| Regions showing **positive** voxel weights (relatively increased activation) | | | | | |
| L Fusiform Gyrus | | 2512 (314) | -34 -34 -24 | 3.74 | |
| R Anterior Lingual/Fusiform Gyrus | | 4304 (538) | 16 -58 -12 | 4.23 | |
| Thalamus | | 256 (32) | 16 -34 2 | 3.48 | |
| PCC/Precuneus | | 10248 (1281) | 0 -28 30 | 4.37 | |
| Superior frontal gyrus (medial) | | 3024 (378) | -4 56 30 | 3.62 | |
| Fronto-Temporal Operculum R | | 312 (39) | 54 8 -2 | 3.57 | |
| Frontal Operculum | | 880 (110) | -56 2 4 | 4.35 | |
| L Middle frontal gyrus | | 352 (44) | -26 52 18 | 3.42 | |
| R Superior Temporal gyrus | | 576 (72) | 50 -34 16 | 3.46 | |
| Caudate | | 472 (59) | -16 -12 26 | 3.24 | |
| x y z are coordinates given in Montreal Neurological Institute (MNI) space. Statistics correspond to a corrected threshold PFDR < 0.05, 10,000 bootstrapping procedure. R, right; L, left. PCC, posterior cingulate cortex. | | | | |

Supplementary Table 4

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Supplementary Table 4. Zero-order bivariate correlations between brain-brain, brain-clinical and clinical-clinical measures in FM patients** | | | | | | | | | | | |
| ***Brain-Brain Correlations*** | | | | ***Clinical-Clinical Correlations*** | | | | | | | |
|  | **NPSp** | **NPSn** | **‘Multisens’ response** |  | | **Functional Impairment** | | **Clinical Pain** | | |
| **NPSp** |  | **0.697**  **(<.0005)** | -0.245 | **Depression** | | **0.601**  **(<.0005)** | | | **0.28 (.093)** | |
| **NPSn** |  |  | 0.030 |
| **FM-pain** | **.390**  **(.017)** | **.392**  **(.016)** | -0.091 | **Funct. Impairm.** | |  | | | **.588 (<.0005)** | |
|  |  |  |  | ***Brain-Clinical Correlations*** | | | | | | | |
|  |  |  |  | **Depression** | **Functional Impairment** | | **Clinical Pain** | | |
|  |  |  | **NPSp** | **0.290**  **(.082)** | 0.224 | | -0.144 | | |
|  |  |  | **NPSn** | **0.333**  **(.044)** | **0.309**  **(.063)** | | -0.064 | | |
|  |  |  | **FM-pain** | 0.159 | 0.091 | | **0.279**  **(.094)** | | |
|  |  |  | **‘Multisens’ response** | -0.053 | 0.031 | | **0.397**  **(.015)** | | |
| The numbers represent Pearson’s r values. Numbers in parenthesis correspond to p-values. Here we report preliminary correlations that need further replication. The correlations are preliminary and require replication in larger samples. | | | | | | | | | | | |

**Supplementary Text 1**

**Rationale for dividing the NPS into the NPSp and NPSn**

We wanted to separate the NPS into NPSp and NPSn components for two reasons. First, historically, there has been debate on whether nociceptive processing is specifically enhanced in FM patients. The original NPS includes a combination of regions targeted by nociceptive afferents, whose activation predicts greater pain, and other heteromodal regions (particularly ‘default mode’ regions) whose activation predicts reduced pain (in the context in which the NPS was developed). Only the former set is likely to be nociception-specific, and we included only those regions in the NPSp. Secondly, based on prior evidence, we hypothesized that the relationship between ‘default mode’ regions and pain is altered in FM patients—specifically, that the relationship between activity and pain becomes more positive in patients—and that the original NPS weights in these regions may not apply. We grouped these regions into the NPSn. Prior work thus led us to have different hypotheses about the NPSp and NPSn: We expected the NPSp to mediate FM-related increases in pain, consistent with enhanced peripheral nociception (e.g., [[19](#_ENREF_19); [20](#_ENREF_20); [22](#_ENREF_22)])) and central sensitization (e.g., [[7](#_ENREF_7); [13](#_ENREF_13); [15](#_ENREF_15); [20](#_ENREF_20); [21](#_ENREF_21)]). By contrast, we expected FM status to moderate (interact with) the relationship between the NPSn and pain, signaling functional alterations in the neurocircuitry of ‘default mode’ regions ([[1](#_ENREF_1); [3-6](#_ENREF_3); [8-12](#_ENREF_8); [14](#_ENREF_14); [15](#_ENREF_15); [18](#_ENREF_18); [23](#_ENREF_23)]).

To estimate NPSp and NPSn pattern responses for each subject, we computed the dot-product of each [Pressure Stimulation – Baseline] contrast image by each of the NPSp and NPSn signature maps. Responses in the NPSp and NPSn consist of a single scalar value that represents a weighted average of activity values across the relevant regions for each subject in each condition.

**Masking procedure to separate the NPSp and NPSn**

The masking procedure described below served the purpose of separating out the NPSp and NPSn regions, which cannot be accomplished by masking out positive and negative voxel weights in the original NPS pattern; the NPS is composed of regions that are overall positive or negative (positively or negative contributing to pain in the original NPS), i.e., showing either positive or negative FDR-corrected peak voxels. However, the pattern of voxel weights in each local region may include both positive and negative voxel values; the procedure below was used to verify that we included all positive and negative NPS weights for each local region.

Therefore, to identify the NPSp, we first identified all positive peak voxels in the original FDR-corrected NPS map (Figure 1 Wager et al. 2013) for nociceptive regions (ACC/SMA, insula, basal ganglia, frontal and parietal opercula, inferior frontal gyrus, thalamus, midbrain and amygdala). Secondly, we applied a smoothing Gaussian kernel of 4-mm FWHM around each NPS positive peak voxel to generate a mask that included all voxels defining the local pattern for those regions. Then, we applied the mask to the original NPS pattern of weights (unthresholded NPS map including all voxel weights). In this way, we warranted the inclusion of all (positive and negative) voxel weights defining the NPS pattern for the ‘nociceptive’ regions (i.e., regions showing FDR-corrected positive peaks—listed above--).

The exact same procedure was used to identify the NPSn. First, we identified the negative peak voxels in the original FDR-corrected NPS map for default-mode network regions (i.e., pgACC/vmPFC and PCC/precuneus/paracentral lobure). Second, we applied a smoothing Gaussian kernel of 4-mm FWHM around each NPS negative peak voxel in ‘default mode’ network regions to generate a mask that included all voxels defining the local patterns for such regions. Then, we applied the mask to the original NPS pattern of voxel weights (unthresholded NPS map including all voxel weights).”

Please note that the NPS pattern of weights that we use here for the NPSp and NPSn regions is the same as in Wager et al. 2013. The difference in colors and scales between Figure 1 in the current manuscript and the original reference reflects the fact that Wager et al. (2013) displayed the FDR-corrected z-scores for visualization purposes, instead of displaying the entire pattern of voxel weights. Here, we display the complete pattern of voxel weights for the included anatomical regions, for completeness. Classification accuracy is indeed computed (both here and in Wager 2013) using the exact same voxel weights within the relevant regions; please see Wager et al. 2013, supplementary information: “The signature weight map applied to Studies 1-3 for diagnostic purposes was not thresholded; all weights were used.

We excluded the voxels in the visual/cerebellar cortex and circumscribed the NPSn to the medial regions, which are the most commonly deactivated regions during experimental pain and constitute regions of interest considering previous studies on chronic pain.

In order to assess local NPS responses, we additionally computed the signature response for each separate contiguous region included in the NPSp and NPSn. Supplementary Table 1 reports the complete list of regions within which local NPS responses were computed.

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**Supplementary Text 2**

**Multivariate pattern-based classification using brain responses to (a) pressure pain and (b) multisensory information.**

We used a linear classifier to maximize interpretability, with a regularization parameter C=1 set *a priori* to reduce over-fitting in both cases (a and b). It is conventional to choose the C parameter *a priori*; the results are often insensitive to this choice within a reasonable range of values[[3](#_ENREF_3)].

We used leave-two-subjects-out cross-validation to estimate classification error, sensitivity and specificity. This approach involves dividing the sample into a training dataset (all but two subjects, one from each group) and a test dataset (the two left-out subjects). SVMs estimated classifier weights for each voxel with the training dataset (a vector of weight values, map) and a scalar offset parameter (analogous to the model intercept). Then predictions about the outcome (patient/healthy: 1/-1) for the left-out test subjects were made by taking the dot-product of the test brain activation map (Tmap) and the signature pattern (map), i.e. (Tmap • map), plus the offset, just as with the NPS. This yielded a scalar value representing the distance from the hyperplane for the test subjects, with a classification boundary of 0. The cross-validation procedure was repeated 35 times (once for each pair of subjects) so that each subject was part of the test dataset exactly once. The misclassification error was then computed as the proportion of participants misclassified.

In order to threshold the resulting map of weights (classification map) for display and interpretation purposes, we performed bootstrap tests. Specifically, we constructed 10,000 bootstrap samples (with replacement)[[2](#_ENREF_2)], and ran SVM on each of these samples. Two-tailed, uncorrected P-values were calculated for each voxel based on the proportion of weights below or above zero[[1](#_ENREF_1)]; we then applied the False Discovery Rate correction for multiple comparisons (*q*<0.05, which produced voxel-wise *p*<0.002).

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**Supplementary Text 3**

**Specific discussion regarding NPSn findings**

*The NPSn pattern* includes patterns within medial regions in which greater *deactivation* was previously associated with increased pain[[24](#_ENREF_24)]. In this study, however, increased pain was associated with greater *activations* in healthy participants (specifically for the PCC/precuneus cluster) and FM patients (for both the PCC/precuneus and the pgACC clusters). Recent work showing structural and functional reorganization in medial PFC in humans[[10](#_ENREF_10); [22](#_ENREF_22)] and animal models of chronic pain (e.g.,[[16](#_ENREF_16); [17](#_ENREF_17)] support this view. The pgACC/ventromedial PFC region has been involved in self-oriented attention[[1](#_ENREF_1)], expectations about pain[[20](#_ENREF_20)], and pain catastrophizing[[21](#_ENREF_21)]. Increased connectivity between this area and the ventral striatum predicts the transition to chronic pain states[[2](#_ENREF_2); [5](#_ENREF_5); [10](#_ENREF_10)], and increased activity predicts spontaneous pain[[4](#_ENREF_4)] and pain-related rumination[[11](#_ENREF_11)] and anxiety[[13](#_ENREF_13)].

In addition, the NPSn may respond differently to different types of noxious stimuli. The NPS was developed using painful heat, whereas here we used painful pressure. Previous studies show that painful pressure applied to the muscle, bone or visceral tissue may significantly engage the PCC/precuneus in healthy subjects[[3](#_ENREF_3); [6](#_ENREF_6); [14](#_ENREF_14); [23](#_ENREF_23)] and (sometimes even to a greater extent) in chronic pain patients with low-back pain, vulvodynia, irritable bowel syndrome and phantom pain[[8](#_ENREF_8); [18](#_ENREF_18); [19](#_ENREF_19); [23](#_ENREF_23); [25](#_ENREF_25)]. These results suggest a different contribution of the PCC/precuneus to the experience of pressure pain vs. thermal pain in both healthy individuals and patients. Both the pgACC and PCC/precuneus are strongly implicated in self-related cognition (e.g., [[1](#_ENREF_1); [7](#_ENREF_7); [9](#_ENREF_9)]); the specific PCC/precuneus region included in the NPSn is functionally connected with other regions of the ‘default mode’ network and also with sensorimotor and attention network regions[[12](#_ENREF_12); [15](#_ENREF_15)]). All in all, we speculate that engaging the NPSn regions may imbue certain pressure (vs. thermal) pain experiences with greater self-referential and sensory qualities, and that greater self-referential activity during pain is a feature of FM and perhaps other chronic pain disorders. Future studies are warranted to explore these issues.

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**Supplementary Text 4**

**Specific discussion regarding medication effects on NPS pattern responses**

We found that antidepressant and anxiolytic medication use was associated with greater NPS responses in patients. Future studies with medication-naïve FM patients would be helpful in disentangling the association between medication status, symptom severity and altered brain responses to pain. However, several considerations suggest that symptom severity may be an underlying cause of both medication use and enhanced NPS responses. First, the relationship between medication use and NPS responses was no longer significant when controlling for symptom severity, suggesting severity as a common cause. In addition, anxiolytics (e.g.[[2](#_ENREF_2),[3](#_ENREF_3)]) and antidepressants (e.g.[[1](#_ENREF_1),[4](#_ENREF_4)]) have been associated with *reduced* brain activation—mostly in the amygdala, insula and ACC—whereas in the present study medication use was associated with *increased* activation in these and other regions. Our observations are therefore contrary to the expected effects of medication use, and suggest that augmented pain-specific responses in medicated patients may reflect greater disease severity.

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