Increased Neural Activation for Conditioned Pain Responses Following a False Low- vs High Pain Cue is Related to Pain Catastrophizing in Fibromyalgia Patients

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Background & Aim

The subjective experience of pain can be altered by associative learning procedures [1,2]. Previous behavioral studies have demonstrated aberrant safety-processing in fibromyalgia (FM), and suggested that patients accumulate new potential pain-related threats more effectively than extinguishing old threats that are not as painful or threatening anymore [1,3,4]. The aim of the current study was to investigate the neural correlates of conditioned pain responses and their relationship to emotional distress in FM and healthy controls (HC).

Method

Subjects (FM *n*=67; HC *n*=34) were scanned with functional magnetic resonance imaging (fMRI) while completing a conditioning paradigm **(Figure 1A, top row)**. In this paradigm, subjects were trained to associate a green and a red cue with pressure (mmHg) corresponding to subjectively calibrated pain ratings of 10mm VAS (P10) and 50mm VAS (P50), respectively. Next, subjects completed the experimental paradigm **(Figure 1A, bottom row)**. In this paradigm, both red and green cues were followed by an identical mid-intensity painful pressure (P30) that corresponded to each subjects' calculated average between P10 and P50, in order to investigate conditioned pain responses in FM and HC **(Figure 1B, 1C)**.

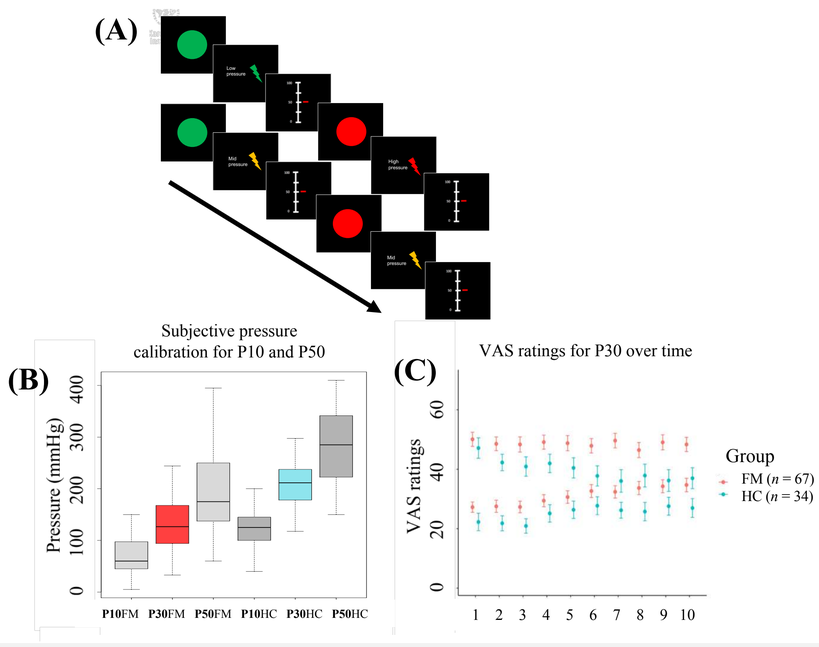

Figure 1

(A) Top row: Exemplifying the conditioning paradigm. **Bottom row:** Exemplifying the experimental paradigm investigating conditioned pain responses in FM and HC. **(B)** Illustrates mean pressure corresponding to subjective ratings of P10, P50; and mid-intensity pressure P30 in FM (red) and HC (cyan). **(C)** Illustrates changes in pain ratings over time in FM (red) and HC (cyan) in response to pressure P30.

Results

Pain ratings varied significantly depending on whether P30 pressure was following a red (P30red) vs. green cue (P30green) (p<.001). FM displayed increased P30green ratings over time, while P30red ratings remained elevated. HC adapted all pain ratings to resemble medium pain **(Figure 3C)**. FM exhibited increased brain activation for [P30green>P30red] in M1/aIns ($p_{(FWE)}$<0.001;z=5.00), whereas HC showed increased S2/aIns response to [P30red>P30green] ($p_{(FWE)}$=0.046;z=3.69) **(Figure 2B)**. High pain catastrophizing ratings (PCS) in FM co-varied with heightened brain activation for [P30green]*PCS in dlPFC ($p_{(FWE)}$=0.021;z=4.24) and vmPFC/OFC ($p_{(FWE)}$<0.001;z=4.06); and [P30green>P30red]*PCS in dACC/MCC ($p_{(FWE)}$=0.003;z=4.67), STP ($p_{(FWE)}$=0.007;z=4.47) extending to bilat. thalamus ($p_{(FWE)}$<0.001;z=4.30), and pIns ($p_{(FWE)}$<0.001;z=4.24) **(Figure 2C)**. Psycho-physiological connectivity for FM[P30green>P30red]*PCS revealed a significant negative task-based interaction between thalamus and bilateral inferior parietal lobe **(Figure 3C)**.

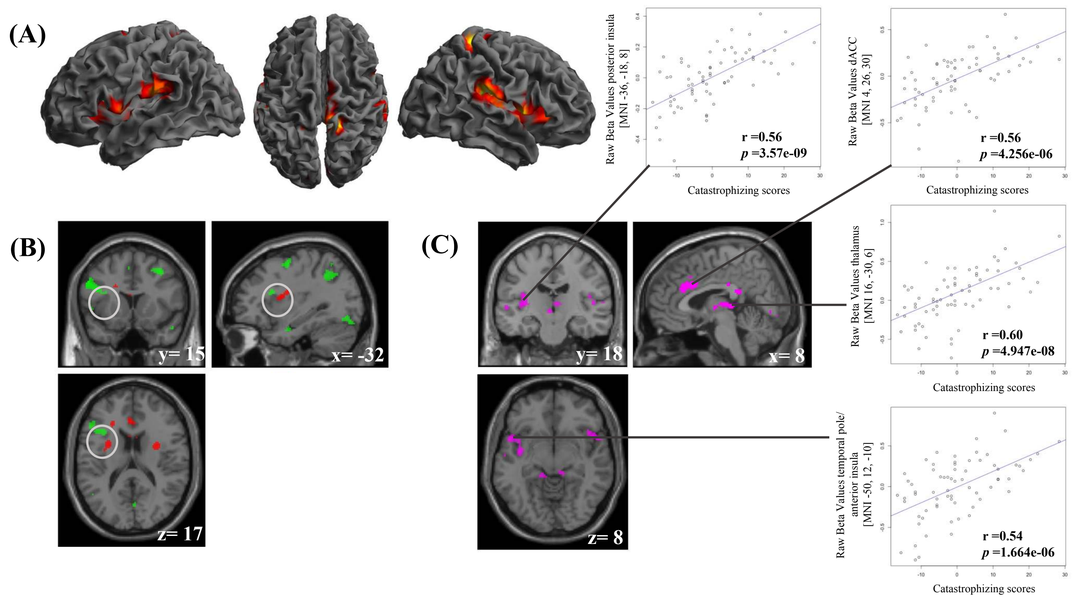

Figure 2

(A) Depicts all participants' brain activation in response to mid-painful pressure (P30), regardless of preceding cue. **(B)** Depicts brain activation in right anterior insular cortex for FM subjects (green) and HC (red) in response to opposing contrasts. **(C)** Demonstrates increased brain activation in FM subjects that significantly co-varied with higher pain catastrophizing ratings for FM[P30green>P30red]*PCS. The correlational plots to the right illustrate extracted raw (unscaled) mean beta weight values from whole clusters of significant brain activation that significantly co-varied with higher pain catastrophizing ratings.

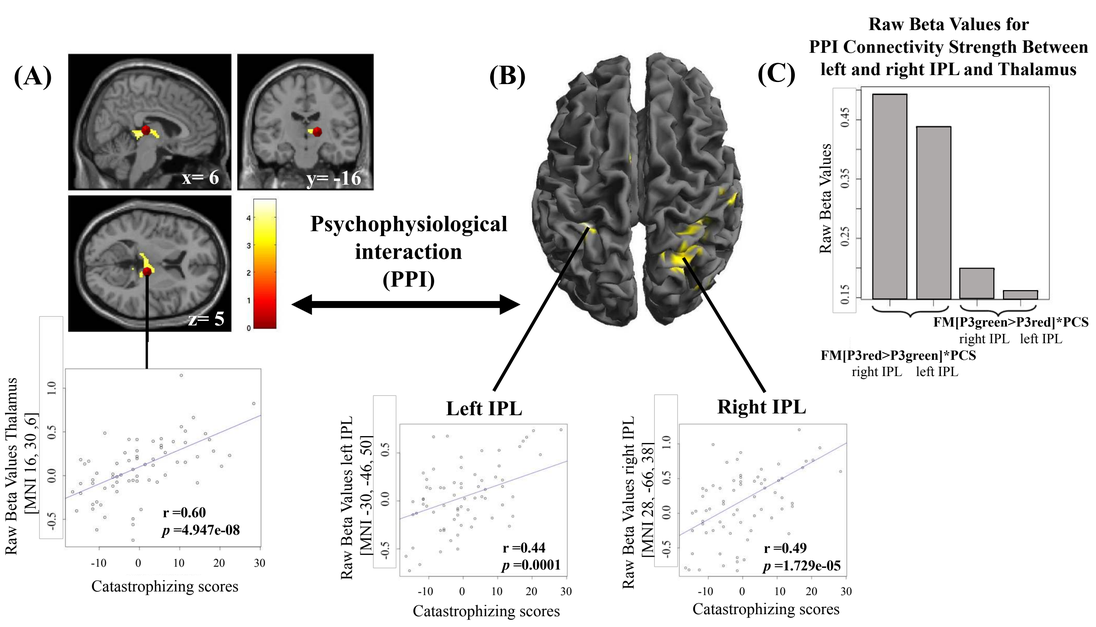

Figure 3

(A) Psychophysiological interaction (PPI) connectivity analysis seeding from right thalamus revealed statistically significant negative interaction in task-based functional connectivity with: **(B)** bilateral inferior parietal lobe (IPL), that significantly co-varied with increased pain catastrophizing ratings in FM subjects when stimulated with identical mid-painful pressure following a green (P30green) or a red (P30red) cue. **(C)** Demonstrates raw (unscaled) beta values for FM task-based connectivity strength (that co-varied with increased pain catastrophizing scores) between right thalamus and bilateral IPL.

Conclusion

In alignment with previous behavioral studies [1,3,4], the current brain imaging data suggests that FM preferentially form new potential pain-related associations rather than extinguishing old, less painful associations. The opposite pattern was found in HC. The effect was even more pronounced among high pain catastrophizing FM subjects. Increased responses to pain-related threats in FM may contribute to dysfunctional pain-protective behaviors and disability.

References: [1] Vlayen, JWS. (2015) *PAIN,156*; [2] Jensen KB., et al. (2015) *PNAS, 112*(25); [3] Jenewein J., et al. (2013) *Eur J Pain, 17*(9); [4] Meulders A., et al. (2015). *PAIN, 156.*

For all fMRI analyses, including PPI, statistical significance was considered for cluster-level family-wise error (FWE) correction for multiple comparisons p<.05 over the entire brain at an initial statistical threshold of p<.001 uncorrected with 20 contiguously activated voxels.

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M1 = primary motor cortex; aIns = anterior insula; S2 = secondary somatosensory cortex; dlPFC = dorsolateral prefrontal cortex; vmPFC = ventromedial prefrontal cortex; OFC = orbitofrontal cortex; dACC = dorsal anterior cingulate cortex; MCC = midcingulate cortex; STP = superior temporal pole