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ORIGINAL RESEARCH

Cerebral responses to innocuous somatic pressure stimulation following aerobic exercise rehabilitation in chronic pain patients: a functional magnetic resonance imaging study

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Objective: The purpose of this research was to assess the functional brain activity and perceptual rating of innocuous somatic pressure stimulation before and after exercise rehabilitation in patients with chronic pain.

Materials and methods: Eleven chronic pain patients and eight healthy pain-free controls completed 12 weeks of supervised aerobic exercise intervention. Perceptual rating of standardized somatic pressure stimulation (2 kg) on the right anterior mid-thigh and brain responses during functional magnetic resonance imaging (fMRI) were assessed at pre- and postexercise rehabilitation.

Results: There was a significant difference in the perceptual rating of innocuous somatic pressure stimulation between the chronic pain and control groups (P=0.02) but no difference following exercise rehabilitation. Whole brain voxel-wise analysis with correction for multiple comparisons revealed trends for differences in fMRI responses between the chronic pain and control groups in the superior temporal gyrus (chronic pain > control, corrected P=0.30), thalamus, and caudate (control > chronic, corrected P=0.23). Repeated measures of the regions of interest (5 mm radius) for blood oxygen level-dependent signal response revealed trend differences for superior temporal gyrus (P=0.06), thalamus (P=0.04), and caudate (P=0.21). Group-by-time interactions revealed trend differences in the caudate (P=0.10) and superior temporal gyrus (P=0.29).

Conclusion: Augmented perceptual and brain responses to innocuous somatic pressure stimulation were shown in the chronic pain group compared to the control group; however, 12-weeks of exercise rehabilitation did not significantly attenuate these responses.

Keywords: fMRI, pain network, central sensitization, BOLD-signal response

Introduction

Chronic pain refers to the persistence of pain beyond the period normally associated with healing from illness or initial injury.[1,2] The level of mechanical somatic pressure stimulation required to produce pain is lower in patients with chronic pain compared to pain-free participants. Previous research has identified a somatic sensitization in patients[3–6] with chronic pain. Allodynia and hyperalgesia have been identified in several chronic pain conditions.[7] A characteristic of central sensitization in chronic pain patients is an enhanced sensitivity to mechanical somatic pressure.[8,9]

Chronic pain has been associated with dysfunctional descending pain inhibition[10,11] and enhanced[12,13] sensitization. Previous research on somatic pressure stimulation in chronic pain patients shows that exercise rehabilitation reduces somatic pressure sensitivity[14] and

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inhibits experimental pain response in patients[15] with chronic pain. The mechanism by which exercise rehabilitation attenuates the sensitivity to somatic pressure is not fully established. However, a plausible basis for the reduced somatic sensitivity in chronic pain following exercise rehabilitation is by a functional restoration of the descending pain-inhibition pathways and/or desensitisation.[16] The insular cortex is one brain site that has common connections with cardiovascular and pain-regulatory functions.[17,18] Additionally, physical exercise may engage central systems associated with pain inhibition.[19] On this basis, exercise rehabilitation may favorably modulate brain responses associated with central sensitization in chronic pain.

Technological advances offer the noninvasive assessment of brain activity in pain research through functional magnetic resonance imaging (fMRI). Previous research has revealed a collection of brain areas that are active during experimental pain stimuli, but not unique to pain.[20] Additional areas of the brain may be recruited to enhance or reduce intensity and unpleasantness.[21] Functional brain imaging in patients with chronic pain has shown several regions of enhanced activity during somatic pressure pain provocation compared to pain-free controls.[22] Prominent brain regions with enhanced neuronal activity include the contralateral primary (S1) and secondary (S2) somatosensory cortices, inferior parietal lobule, cerebellum, and ipsilateral S2 in chronic pain patients.[22] The same somatic pressure stimulus resulted in only a single activation in the contralateral S2 in pain-free controls. Additional areas of enhanced brain activity have been observed in the basal ganglia, operculo-insula, inferior parietal cortex,[23] and the prefrontal cortex,[20] but these may be active depending on the set of circumstances.

Few studies have ascertained functional brain responses during innocuous somatic pressure stimulation in chronic pain.[24] In order to further elucidate brain activation in chronic pain, innocuous somatic pressure may reveal brain regions that are active under central sensitization. Areas of enhanced neuronal activity during innocuous stimulation have been previously observed in the medial frontal gyrus, insula, superior temporal gyrus, cerebellum, sensory cortex, and the cingulate.[24] Therefore, the purpose of this study was to compare perceptual and functional brain responses to innocuous somatic pressure in patients with chronic pain and pain-free controls. We also examined for mediation of perceptual and brain responses to somatic pressure stimulation during fMRI after 12 weeks of aerobic exercise rehabilitation.

Materials and methods

The participants included eleven patients with chronic pain disorder (nine women and two men) and eight healthy control participants (seven women and one man). Participants with chronic pain included eight subjects with fibromyalgia, two with back pain, and one individual with complex regional pain. Chronic pain patients were diagnosed by a general medical practitioner, rheumatologist, or pain specialist with persistent pain for a period of at least 12 months prior to participating in the study. All participants were screened with a physical activity-readiness questionnaire.[25] The exclusion criteria for chronic pain participants were persons with acute inflammatory conditions, acute pain, cancer pain, and inability to perform moderate-intensity aerobic exercise. The healthy control participants were required to be pain-free and have no illness or disease.

The study was conducted with the approval of the University Ethics in Human Research Committee (approval 08/07) and Area Health Ethics in Human Research Committee 2008/5/4.23 (2753). Participants were provided with study information, and signed a letter of informed consent prior to research participation.

All chronic pain patients reported regular use of nonprescription anti-inflammatory and analgesic medications, four reported using prescription opioid-based medicine, and three chronic pain participants were using prescription medication for mild depression. The chronic pain patients maintained their regular medication during the course of the study; however, they abstained from medication for 12 hours prior to functional brain imaging.

Experimental design

The design of the study is a comparative age-matched cross section involving within- (pre- and postexercise intervention) and between- (chronic pain and control)-group analyses. Exercise intervention was performed by both the chronic pain and control participants, and comprised 20 minutes of supervised aerobic exercise twice per week over 12 weeks. The body mass index (BMI), health status (Short Form [36] Health Survey [SF-36] total),[26] and pain appraisal (McGill Pain Questionnaire [MPQ] total score)[27] were assessed prior to the exercise rehabilitation program. Exercise modalities included aerobic activity of treadmill walking or stationary cycling. Cardiovascular fitness was assessed before and after aerobic rehabilitation by heart-rate (HR) response to a standard submaximal exercise power output (HR/W).

Functional magnetic resonance imaging acquisition

Participants were imaged on a 3T GE Signa Excite MRI scanner (GE Healthcare, Little Chalfont, UK) with an eight-channel MRI Devices (Waukesha, WI, USA) head coil. The

fMRI utilized a single-shot echo planar imaging sequence (TR-3000 ms, TE-35 ms, 24 cm field of view, 4 mm slices, 39 slices, 128× 128 matrix). The fMRI procedure was a block-design paradigm consisting of five rest and five stimulus periods of 30 seconds each. Coronal 3-D spoiled gradient-echo and T2 axial datasets were also acquired for structural brain information. Imaging was performed within 2 weeks prior to aerobic exercise rehabilitation and within 1 week after aerobic exercise rehabilitation.

Mechanical somatic pressure stimulation

Somatic pressure stimulation was applied during the fMRI procedure. The somatic pressure consisted of a 2 kg mass with a flat surface-contact diameter of 2 cm positioned on the anterior surface of the right mid-thigh. This location was marked at the midpoint between the superior aspect of the patella and mid-inguinal fold. The pressure stimulus at this site elicited a dull compression of the tissues between the superior surface of the thigh and femur. Participants were requested to rate the somatic pressure sensation on the mid-thigh using a 0–10 sensory category-ratio scale[28] immediately following the fMRI scanning procedure. The numerical anchors and verbal descriptors were graded as 0= no sensation, 2= slight sensation, 4= moderate sensation, 6= pain sensation, 8= strong pain sensation, and 10= pain tolerance. Prior to each fMRI scanning procedure, participants were familiarized with the numerical anchors and descriptors of the sensory scale.

Image processing and analysis

Images were processed using MatLab version 7.11 (MathWorks, Natick, MA, USA) and Statistical Parametric Mapping (SPM)-8 software (Wellcome Trust Centre for Neuroimaging, London, UK). Data preprocessing consisted of motion correction using realignment, normalizing to standard Montreal Neurological Institute space, and smoothing using an 8 mm Gaussian kernel. Data were filtered using a high-pass filter (cutoff period of 128 seconds).

Preprocessed images for individual participants were then analyzed in a first-level fixed-effects analysis using a canonical hemodynamic response-convolved box-car function to model the blood oxygen-dependent (BOLD) response during stimulus. A contrast image of stimulus versus rest was derived for each participant at each time point.

Whole-brain analysis was performed by repeated-measures analysis of variance (ANOVA) within the SPM8 General Linear Model framework with group (chronic pain and control) as the between-subjects factor and time point (before and after) as the within-subjects factor. Error correction (false-discovery rate) for multiple comparisons using a height threshold of $P<0.05$ was performed. Spatial coordinates from the obtained maps were ascertained hierarchically to the nearest gray matter in Talairach space.[29] Sites showing significant or trends for main group effects (chronic pain versus control) in the whole-brain analysis were further assessed by a region of interest (ROI) approach. BOLD signal change for each ROI was extracted from individual participant data at pre and post-aerobic exercise rehabilitation using a MarsBaR (MARSeille Boîte À Région d'Intérêt) toolbox.[30] The ROIs comprised 5 mm radii around the peak-cluster coordinates, as identified in whole-brain analysis.

Statistical analysis

Repeated-measures ANOVA was performed for the somatic pressure rating, aerobic fitness (HR/W), and the BOLD signal change in the ROIs. Group comparisons were performed for SF-36 total health score and BMI.

Results

Group characteristics

Characteristics including BMI, MPQ pain score, SF-36 total health status for the chronic pain and control groups (mean ± standard deviation [SD]) are shown in Table 1. Group comparisons between the chronic pain and control groups revealed a significant difference for BMI ($P<0.01$) and for SF-36 total health status ($P<0.001$). Repeated measures showed a significant difference in HR/W between groups ($P=0.05$), and there was a significant improvement in aerobic fitness (HR/W) for the chronic pain and control groups following exercise rehabilitation ($P<0.001$).

Perceptual responses to somatic pressure stimulation during fMRI

The perceptual rating of a standard 2 kg weight on the right mid-thigh was assessed to confirm somatic pressure hypersensitivity in the chronic pain group. The mean perceptual ratings (sensory scale units ± SD) to the somatic pressure stimulus during the fMRI scanning procedure for the chronic

Table 1 Group characteristics prior to aerobic exercise rehabilitation

	Chronic pain	Control group
Age (years)	50.0±12	49.6±10
BMI*	34.9±7	27.6±2.1
MPQ total	19.2±11.7	0
SF-36 total*	29.6±15.3	76.7±12.1

Notes: Data are presented as means ± standard deviation. *Group comparisons between chronic pain and control groups ($P<0.05$).
Abbreviations: BMI, body mass index; MPQ, McGill Pain Questionnaire; SF-36, Short Form (36) Health Survey.

pain and control groups at pre- and post-aerobic exercise rehabilitation are shown in Figure 1. The chronic pain group revealed a 46% elevated perceptual rating compared to the control group during fMRI to the somatic pressure stimulus at pre-aerobic exercise rehabilitation, and 50% higher perceptual rating at post-aerobic exercise rehabilitation. Results for repeated-measures ANOVA revealed a significant difference between chronic pain and control groups for the perceptual rating of the somatic pressure stimulus (P=0.01), but no group-by-time interaction.

fMRI whole-brain analysis

Whole-brain voxel-wise analyses for between groups (chronic pain and control) are shown in Table 2. The associated images are shown in Figure 2. None of these tests survived multiple comparisons for the whole brain (threshold $P<0.05$); however, we have listed sites showing trends between the chronic pain and control groups. We report these findings as preliminary results given the small sample size.

BOLD signal changes in the regions of interest (pre- versus postexercise rehabilitation)

The BOLD signal change in the ROIs for the chronic pain and control groups at pre- and postexercise (± SD) are shown in Figure 3. Repeated-measures ANOVA showed a significant difference between groups (P=0.04). Group comparisons for the ROIs revealed trend differences in the superior temporal gyrus (P=0.06), thalamus (P=0.04), and caudate (P=0.21). Contrasts for time revealed some trend differences in the superior temporal gyrus (P=0.29), thalamus (P=0.12), and caudate (P=0.37). Trends for group-by-time interaction within the ROIs were seen in the caudate (P=0.10) and superior temporal gyrus (P=0.29).

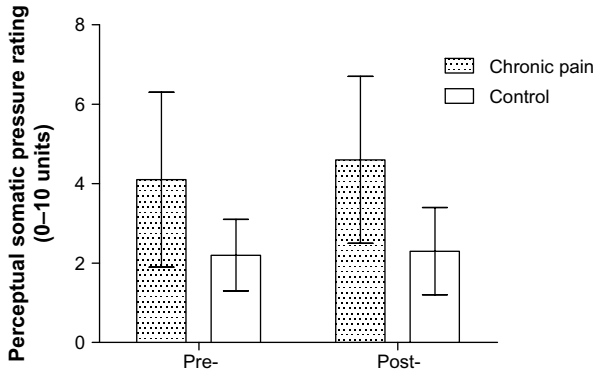

Figure 1 Mean (± standard deviation) perceptual rating (0–10 units) of somatic pressure stimulation during functional brain imaging for chronic pain and control groups at pre- and post-aerobic exercise rehabilitation.
Note: There was a significant difference between groups (P=0.01).

Discussion

The present study hypothesized that aerobic exercise rehabilitation would reduce the perceptual rating and brain responses to mechanical somatic pressure stimulation (reduced central sensitization) in the chronic pain group. Following the exercise rehabilitation program, both groups showed enhanced cardiovascular fitness. However, the perceptual rating of the somatic pressure in the chronic pain group was not statistically different after the aerobic exercise rehabilitation. The main findings in the fMRI results show differences in brain responses between the chronic pain and control groups during innocuous somatic pressure stimulation in the right superior temporal gyrus, right thalamus, and left caudate (Table 2 and Figure 3).

Perceptual rating of innocuous somatic pressure stimulation

Previous research shows that the perceptual rating of somatic pressure stimulation is elevated in patients with chronic pain compared to pain-free control participants.[23] In the present results, enhanced perceptual rating of the innocuous somatic pressure (Figure 1) indicated somatosensory augmentation and central sensitization in the chronic pain group. The mechanism underlying central sensitization in chronic pain may be associated with enhanced activity from low-threshold cutaneous mechanoreceptive fibers.[5] Additionally, previous research has revealed a relationship between increased bodyweight status and enhanced pain sensitivity in chronic pain patients.[31,32] Results in the present study showed a significant difference in BMI between the chronic pain group and control group, and this may have contributed to the elevated perceptual rating of the innocuous somatosensory stimulus. The mechanism underlying the relationship between bodyweight status and pain sensitivity in chronic pain patients has not been fully elucidated, although increased proinflammatory markers in overweight patients may be associated with enhanced pain sensitivity.[33]

Previous studies have shown a reduction in the perceptual rating of noxious mechanical somatic pressure in chronic pain patients following exercise rehabilitation.[14] The present study investigated the effects of innocuous somatic pressure ratings following exercise rehabilitation. However, the perceptual rating of the innocuous somatic pressure in the present study did not reveal a reduced perceptual response. One possible explanation for this outcome is that the exercise rehabilitation

Table 2 Whole-brain voxel-wise analysis, showing sites for elevated trends between the chronic pain and control groups

	MNI coordinates	Cluster size	Uncorrected *P*-value	Corrected *P*-value	Site
Chronic > control	44, 12, −14	83	$P<0.001$	$P=0.39$	Right cerebrum, temporal lobe, superior temporal gyrus
Control > chronic	−8, 16, 14	18	$P<0.001$	$P=0.23$	Left cerebrum, sublobar, caudate, gray matter, caudate body
	12, −36, 12	34	$P<0.001$	$P=0.23$	Right cerebrum, sublobar, thalamus, gray matter, pulvinar

Abbreviation: MNI, Montreal Neurological Institute.

period was not sufficient to develop significant changes in central sensitization. Further research could increase the intervention period and monitor changes in somatic pressure sensation and brain responses during exercise rehabilitation within a larger sample of chronic pain patients.

Superior temporal gyrus

Brain regions that revealed differences between the groups included the right superior temporal gyrus, left caudate, and the right thalamus (Table 2). Notably, neuronal activity from the somatosensory area was not prominent in the chronic pain group. This suggests that differences in brain responses during the innocuous somatic pressure were more associated with activity in regions not involved in somatosensory processing, but with regions involved with anticipation and emotion. A prominent brain region involved in anticipation is the entorhinal complex,[34] which includes neuronal areas in the medial temporal lobe.[35] Previous research has shown direct projections between the superior temporal gyrus and the entorhinal cortex.[36] The superior temporal gyrus featured prominently in the present results in the chronic pain group, and this has previously been observed in chronic pain patients.[24] From this, the increased anticipation and activity from the superior temporal gyrus during the mechanical somatic pressure stimulation partially explains the elevated perceptual ratings in the chronic pain group compared to the control group. However, the response of the superior temporal gyrus was not attenuated following the aerobic exercise rehabilitation. Previous experimental pain studies have shown that anxiety-related increases in perceived pain are associated with activation in the entorhinal cortex of the hippocampus.[35] Therefore, the increased activity in the superior temporal gyrus in the chronic pain group at the postexercise-rehabilitation period may have been associated with enhanced anticipation during the innocuous stimulation procedure.

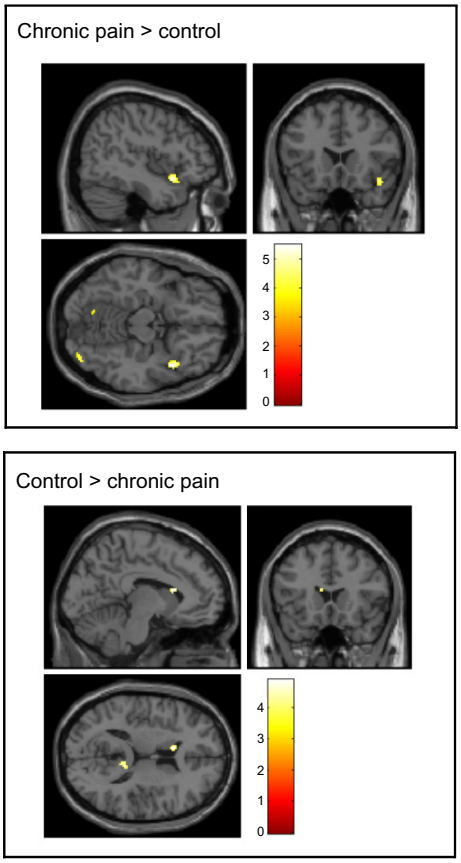

Figure 2 Brain regions showing enhanced neuronal responses to innocuous somatic pressure stimulation between the chronic pain group and the control group.
Note: Activations are shown at an uncorrected $P<0.001$ threshold. The right superior temporal gyrus, right thalamus, and left caudate showed trend differences after correction for multiple comparisons. Color bars represent t-scores.

Thalamus

The present results showed a significant difference in the BOLD signal within the thalamus in the chronic pain group compared to the control group (Figure 3). Enhanced thalamic activity has been shown in pain-free healthy participants compared to patients with chronic pain during noxious stimulation.[24] Moreover, regional blood flow[37,38] and neuronal activity[10] in the thalamus has been shown to be reduced in chronic pain patients compared to controls. It has previously been suggested that thalamic response is inhibited in chronic pain due to a functional plasticity from persistent pain signaling. This is supported by research showing that

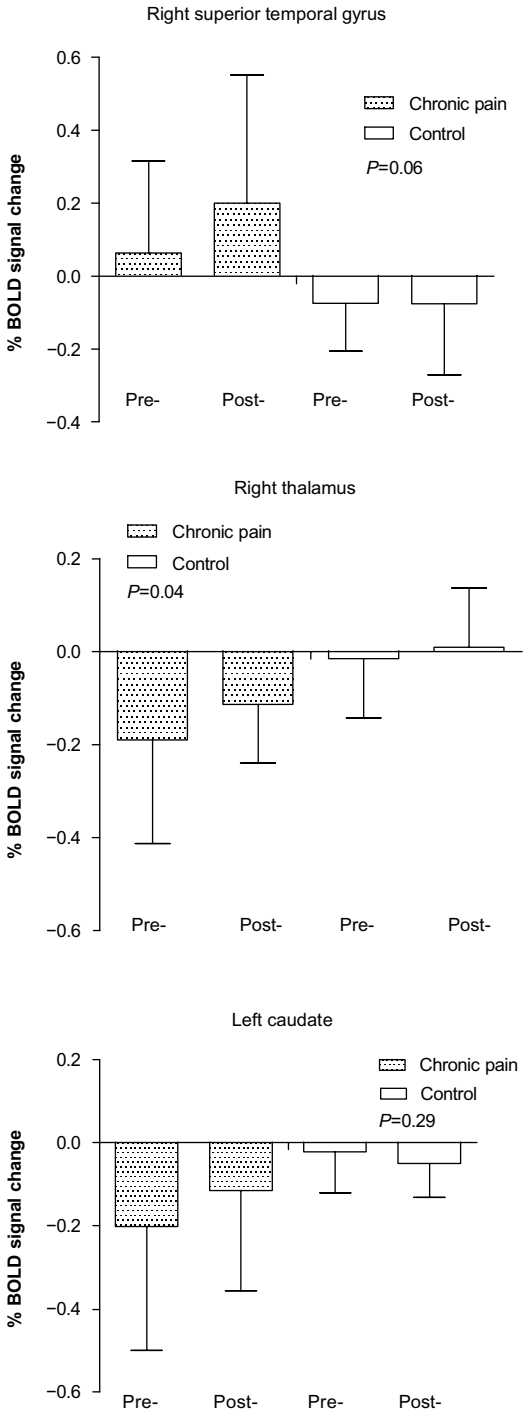

Figure 3 Percentage blood oxygen level-dependent (BOLD) signal changes (means ± standard deviation) between chronic pain patients and controls within the right superior temporal gyrus, thalamus, and caudate at pre- and post-aerobic exercise rehabilitation.
Note: *P*-values are shown for repeated-measures group comparisons.

reduced thalamic activity was enhanced following analgesic treatment in chronic pain patients.[39]

Caudate

The present results revealed that neuronal activity in the caudate was reduced in the chronic pain group compared to the control group (Table 2 and Figure 3). In accord with this, previous research has shown that regional blood-flow activity in the caudate is reduced in chronic pain participants compared to controls.[38] Enhanced activity in the caudate has previously been observed in healthy controls compared to chronic pain participants,[24] although this difference was not observed in another study using cerebral blood-flow analysis.[37] In previous pain research, activation in the caudate suggested that this may be a likely source for pain inhibition.[40] The suppression of the feeling of pain has also been shown by activation of the caudate.[41] The present results showed some improvement in caudate response following exercise rehabilitation in the chronic pain group, although this was not statistically significant. Therefore, the present findings suggest a functional abnormality in the caudate during innocuous somatic pressure stimulation in patients with chronic pain.

Study limitations

Limitations in the present study include the small sample and the degree of variance in the duration of persistent pain in the patient group. Previous research has shown that persistent pain is associated with neurodegenerative changes, and that this corresponds with the duration of chronic pain.[42] The present study included patients with a duration of chronic pain of greater than 1 year. This may have provided a heterogeneous sample and influenced the effects of exercise rehabilitation. It is possible that the chronic pain patients may have had progressive neurodegenerative changes within the duration of the study. Also, the intervention period may not have been sufficient to substantially mediate brain responses in the chronic pain group, although there was some trend shown in the caudate. Pain medication could alter brain responses, although none of the chronic pain patients reported substantial changes during the study and prior to the brain-scanning procedure. Future studies could provide a more homogeneous duration of chronic pain patients and extend the exercise-intervention period.

Affective and cognitive factors, such as attention, anxiety, and anticipation, may mediate the perception of somatosensation. Within the present study, the influence of central factors, such as emotion and cognitive components, was not assessed. In one study, anxiety and depression were cofactored among participants, and this revealed that cognitive and affective factors during the anticipation of pain played an important role in pain processing.[4] It has been suggested that attentional mechanisms, such as hypervigilance, may influence the evoked cerebral response in structures similar to those observed in the present study.[24]

Conclusion

The present study showed that innocuous somatic pressure stimulation in the chronic pain patients revealed elevated perceptual ratings and enhanced brain activity compared to the pain-free control group. Innocuous somatic pressure stimulation resulted in differences in brain responses within the superior temporal gyrus, thalamus, and caudate. Exercise rehabilitation did not reveal a significant reduction in the perceptual rating to innocuous stimulation in the chronic pain group; however, there was some trend toward improved BOLD-signal response in the caudate. In contrast, there was an enhanced response in the superior temporal gyrus within the chronic pain group, which may have been associated with increased anticipation. These observations of augmented perceptual and brain responses lead toward further understanding of the consequences of chronic pain and the effects of exercise rehabilitation.

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Disclosure

The authors report no conflicts of interest in this work.

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