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The effects of a 15-week physical exercise intervention on pain modulation in fibromyalgia: Increased pain-related processing within the cortico-striatal- occipital networks, but no improvement of exercise-induced hypoalgesia

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ABSTRACT

Dysfunctional top-down pain modulation is a hallmark of fibromyalgia (FM) and physical exercise is a cornerstone in FM treatment. The aim of this study was to explore the effects of a 15-week intervention of strengthening exercises, twice per week, supervised by a physiotherapist, on exercise-induced hypoalgesia (EIH) and cerebral pain processing in FM patients and healthy controls (HC). FM patients (n = 59) and HC (n = 39) who completed the exercise intervention as part of a multicenter study were examined at baseline and following the intervention. Following the exercise intervention, FM patients reported a reduction of pain intensity, fibromyalgia severity and depression. Reduced EIH was seen in FM patients compared to HC at baseline and no improvement of EIH was seen following the 15-week resistance exercise intervention in either group. Furthermore, a subsample (Stockholm site: FM $n = 18$; HC $n = 19$) was also examined with functional magnetic resonance imaging (fMRI) during subjectively calibrated thumbnail pressure pain stimulations at baseline and following intervention. A significant main effect of exercise (post > pre) was observed both in FM patients and HC, in pain-related brain activation within left dorsolateral prefrontal cortex and caudate, as well as increased functional connectivity between caudate and occipital lobe bordering cerebellum (driven by the FM patients). In conclusion, the results indicate that 15-week resistance exercise affect pain-related processing within the cortico-striatal-occipital networks (involved in motor control and cognition), rather than directly influencing top-down descending pain inhibition. In alignment with this, exercise-induced hypoalgesia remained unaltered.

Abbreviations: AAL, Automated Anatomical Labeling; ACR, American College of Rheumatology; CNS, central nervous system; CPM, conditioned pain modulation; dlPFC, dorsolateral prefrontal cortex; EIH, exercise-induced hypoalgesia; FD, Frame-wise displacement; FIQ, Fibromyalgia Impact Questionnaire; FM, fibromyalgia; fMRI, functional magnetic resonance imaging; FOV, field of view; FEW, family-wise error; FWHM, full-width-half-maximum; GLM, general linear model; HADS, Hospital Anxiety and Depression Scale; HC, healthy controls; MNI, Montreal Neurological Institute; MVC, maximum voluntary contraction force; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, psychophysiological interaction; PPTs, pressure pain thresholds; P50, pressure stimuli corresponding to a pain rating of 50mm on a 100 mm VAS; rACC, rostral anterior cingulate cortex; RM, repetition maximum; SM, stimulation maximum; SPM, Statistical Parametric Mapping; T1, longitudinal relaxation time; T2, transverse relaxation time; TR/TE, time repetition/time echo; VAS, visual analogue scale; VOI, volume of interest.

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Introduction

Fibromyalgia (FM) is a common chronic pain syndrome characterized by widespread, mainly muscular pain, hypersensitivity, disturbed sleep and fatigue. The pathophysiology is complex and ranges from peripheral nerve pathology (Üçeyler et al., 2013; Serra et al., 2014), dysfunction of the sympathetic nervous system (Cohen et al., 2001; Kadetoff and Kosek, 2010), neuroinflammation (Backryd et al., 2017; Kadetoff et al., 2012) and glia cell activation (Albrecht et al., 2019) to muscle abnormalities. The documented aberrations in skeletal muscle include unspecific morphological signs of muscle ischemia, derangements in muscle metabolism, and reduced capillary muscle blood flow during physical activity (Elvin et al., 2006; Gerdle et al., 2016; Ruggiero et al., 2018). However, the common view is that pain in FM is mainly explained by altered nociceptive processing in the central nervous system (CNS), and FM is regarded as a prototype of nociplastic pain (Kosek et al., 2021; Kosek et al., 2016). Altered nociception in FM is indicated by reports of increased temporal summation (O'Brien et al., 2018), dysfunction of descending pain modulation, i.e., exercise-induced hypoalgesia (EIH) and conditioned pain modulation (CPM) (O'Brien et al., 2018; Kosek et al., 1996; Kosek and Hansson, 1997; Lannersten and Kosek, 2010). The complicated pathophysiology is reflected in the lack of effective treatment options. Current FM treatment relies on patient education, physical exercise, pharmacological treatments, cognitive behavioral therapy and multi-professional rehabilitation programs (Macfarlane et al., 2017).

The only treatment for FM that received a "strong for" recommendation in the latest European guidelines was physical exercise (Macfarlane et al., 2017). Multiple studies have reported beneficial effects of aerobic exercise (Bidonde et al., 2017; Häuser et al., 2010; Andrade et al., 2020). However, less is known about strength training (Busch et al., 0000; Figueroa et al., 2008; Andrade et al., 2018; Larsson et al., 2015) and very little is understood regarding the beneficial physiological effects of exercise in FM (Ortega et al., 2009; Steiger et al., 2012; Sluka et al., 2018).

In pain-free populations, a single bout of resistance exercise reduces pain sensitivity, an effect known as EIH (Kosek et al., 1996; Kosek and Lundberg, 2003; Rice et al., 2019), and EIH has been reported to be more pronounced in physically active healthy individuals (Ohlman et al., 2018; Schmitt et al., 2020). In addition, physically active healthy women have been reported to be less pain sensitive than those who are sedentary (Ellingson et al., 2012). An important question, that remains unexplored, is whether long-term physical activity would reduce pain sensitivity by enhancing the efficacy of EIH in patients with dysfunctional EIH, such as FM patients.

We wanted to profit from our cohort of FM patients and HC participating in an assessor-blinded randomized controlled multi-center trial examining the effects 15 weeks of progressive strength exercise compared with an active control group (ClinicalTrials.gov identification number: NCT01226784). The primary aim of this study was to assess if the standardized, 15-week strength exercise intervention improved EIH in FM patients and HC, respectively. The secondary aim was to explore the effects of the strength exercise intervention on cerebral pain processing. Based on previous studies (Rice et al., 2019), we expected to find reduced EIH in FM patients compared to HC at baseline. Our hypothesis was that the exercise intervention would improve EIH in FM patients, thus partly explaining the reduced pain intensity previously reported following the exercise intervention in these FM patients (Larsson et al., 2015).

The physiology underlying EIH is complex and not fully understood (Rice et al., 2019), but opioid mechanisms seem to have no or limited effects on EIH in HC or FM patients (Tour et al., 2017). On the contrary, previous neuroimaging studies assessing cerebral processing of evoked pressure pain in FM, compared to HC, revealed an inability to activate the rostral anterior cingulate cortex (rACC), an opioid rich area and a primary link in the descending pain regulatory system (Jensen et al., 2009; Jensen et al., 2013). Furthermore, the reduced activation of ACC during evoked pressure pain in FM was associated with lower μ-opioid receptor binding capacity in that region (Schrepf et al., 2016). As EIH mainly relies on non-opioid mechanisms, we consider it unlikely that the opioid-linked dysfunctions of cerebral pain modulation previously documented in FM patients would explain their inability to activate EIH, nor would they likely be linked to a potential improvement of EIH following exercise. Therefore, our assessment of the effects of physical exercise on cerebral pain processing is to be regarded as purely exploratory.

Material and methods

Subjects

Subjects were recruited through newspaper advertisement to participate in a multicenter study performed at 3 sites in Sweden: Gothenburg, Linköping and Stockholm (ClinicalTrials.gov identification number: NCT01226784). The participants were randomized to resistance exercise training or relaxation therapy (Larsson et al., 2015). The randomization was conducted separately for each site in blocks of six subjects by a computer generated sequence. For each participant the treatment was concealed in sequentially numbered, sealed, opaque envelopes. Randomization and concealment was done by a person not involved in the examinations or treatments (ME).

When a participant had been included the envelope was opened together with each participant, after which she was informed about the group to which she had been allocated. A total of 122 female participants (FM $n = 78$; healthy controls, HC $n = 44$) were randomized to resistance exercise training and thus eligible for the current study. See flowchart (Fig. 1) for complete participant recruitment process.

Exercise intervention cohort

The exercise intervention cohort refers to all participants who

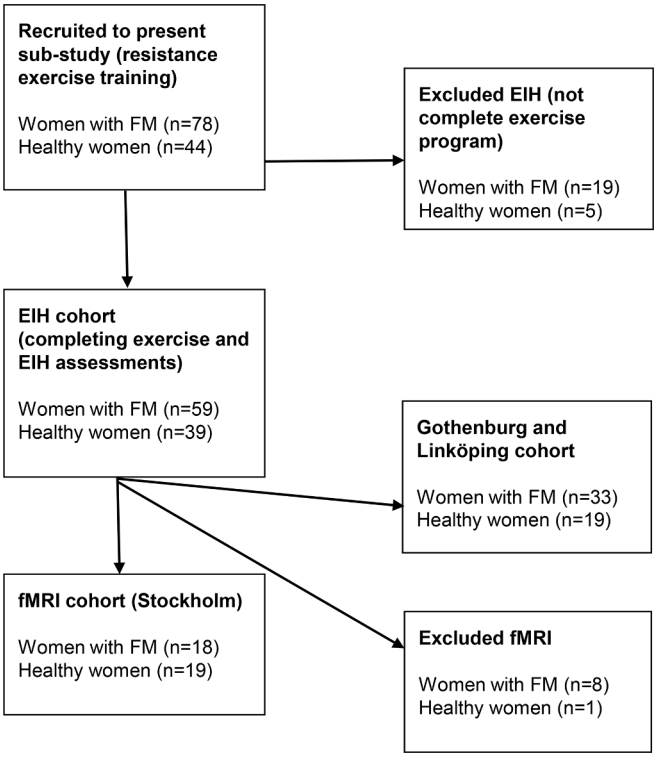

Fig. 1. Flow-chart of the recruitment process of the Exercise-induced hypoalgesia (EIH) cohort and the functional magnetic resonance imaging (fMRI) cohort.

completed the physical exercise intervention and the assessments of exercise-induced hypoalgesia (EIH) before and after the intervention at any of the three sites (Gothenburg, Linköping and Stockholm). Initially, 78 FM patients were enrolled and 19 patients dropped out from the intervention, leaving a final FM sample that completed the pre/post exercise intervention and pre/post EIH assessments of 59 FM patients (median age = 51 y) with a median duration of FM of 9 years. For further background data on the FM patients and healthy controls, see Table 1.

Forty-four healthy controls (HC) initially enrolled in the exercise intervention at any of the three sites, and five HC dropped out. Hence, the final HC sample consisted of 39 subjects (median age = 56 y) that completed the pre/post exercise intervention and pre/post EIH assessments.

Functional magnetic resonance imaging (fMRI) subsample. Only participants at the Stockholm site and randomized to the exercise intervention, were also scanned with functional magnetic resonance imaging (fMRI) before and after the intervention. Hence, the fMRI participants constitute a subsample of the total exercise intervention cohort. Twenty-six FM patients were scanned with fMRI at baseline. Of those, eight patients were excluded in the current study due to not completing the post intervention fMRI (e.g. pregnancy, $n = 1$); technical failure post intervention ($n = 2$); and due to unwillingness to participate in the second fMRI ($n = 5$). Hence, the final fMRI sample consisted of 18 FM patients (median age = 50) with a median FM duration of 8 years.

Twenty HC at the Stockholm site were enrolled to participate in fMRI scan. One participant was excluded due to brain anomalies, resulting in the final cohort consisting of 19 healthy participants for fMRI analysis (median age = 55 y).

Inclusion and exclusion criteria. The current study was planned and initiated in 2009 (i.e. before the 2010 criteria were recognized) (Larsson et al., 2015). Hence, the American College of Rheumatology (ACR) 1990 criteria was used. FM patients were physically examined by a specialist in rehabilitation medicine to ensure that they fulfilled the inclusion criteria and did not fulfil any exclusion criteria. Inclusion criteria for women with FM were to be of working age (i.e. 20–65 years), meeting the ACR-1990 classification criteria for FM (Wolfe et al., 1990) and no other primary cause of pain than FM. Healthy participants were screened on the telephone. Inclusion criteria for HC were to be of female sex, pain-free and of working age (i.e. 20–65 years) (Larsson et al., 2015).

Exclusion criteria for both groups were high blood pressure (>160/90 mmHg); osteoarthritis in hip or knee; other severe somatic or psychiatric disorders; high consumption of alcohol (AUDIT score >6); participation in a rehabilitation program within the past year; regular resistance exercise training or relaxation exercise training twice a week or more; inability to understand or speak Swedish; and not being able to refrain from analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) or hypnotics for 48 h prior to examinations. All participants declared that they had refrained from hypnotics, NSAIDs, acetaminophen and tramadol/other analgesics at least 48 h prior to study participation (48 h before EIH and 72 h before fMRI) (Larsson et al., 2015).

Table 1
Background variables. EIH = Exercise-Induced Hypoalgesia, fMRI = functional Magnetic Resonance Imaging, FM = fibromyalgia patients, HC = healthy controls, BMI = Body Mass Index.

Cohort	Variable			Group diff p-value
EIH cohort	**Age years** (median, 25–75 %)	FM	51 (46–58)	
		HC	56 (42–60)	0.511
	Weight kg (median, 25–75 %)	FM	73 (64–87)	
		HC	64 (60–74)	0.006
	BMI (median, 25–75 %)	FM	26 (23–31)	
		HC	24 (21–25)	0.004
	Blood pressure systolic (median, 25–75 %)	FM	125 (115–140)	
		HC	126 (120–140)	0.940
	Blood pressure diastolic (median, 25–75 %)	FM	84 (75–85)	
		HC	85 (77–89)	0.365
fMRI subsample	**Age years** (median, 25–75 %)	FM	50 (44–57)	
		HC	55 (40–58)	0.433
	Weight kg (median, 25–75 %)	FM	68 (65–81)	
		HC	69 (60–78)	0.655
	BMI (median, 25–75 %)	FM	24 (23–26)	
		HC	25 (22–30)	0.985
	Blood pressure systolic (median, 25–75 %)	FM	125 (120–160)	
		HC	129 (119–140)	0.864
	Blood pressure diastolic (median, 25–75 %)	FM	85 (80–95)	
		HC	86 (80–90)	0.909

Procedure

The study protocol consisted of 2 visits for participants at Gothenburg and Linköping and 6 visits for the Stockholm cohort (apart from the exercise intervention program and screening). During the first visit, participants at all sites completed questionnaires and assessments of pressure pain thresholds (PPTs) as well as EIH. This procedure was identically repeated following the 15-week exercise intervention.

The Stockholm cohort had 4 additional visits related to the fMRI scanning. Two visits were performed at the MR Center in Stockholm before the exercise intervention. The first for individual pressure pain calibration for fMRI and the second for the fMRI session. The same procedure was then repeated during the two visits at MR Center following the 15-week exercise intervention.

Questionnaires

The following questionnaires were selected among those collected at baseline and at the post-intervention test (Larsson et al., 2015): Current pain intensity was rated on a 0 to 100 visual analogue scale (VAS), anchored from 0 = "no pain" and 100 = "worst imaginable pain". FM patients rated the impact of fibromyalgia with the Fibromyalgia Impact Questionnaire (FIQ), a disease-specific questionnaire with 10 sub-scales; a higher score indicates a lower health status (Bennett, 2005). Symptoms of anxiety and depression were measured by the Hospital Anxiety and Depression Scale (HADS) (Bjelland et al., 2002); a higher score indicates more symptoms.

Pressure pain thresholds

A hand-held electronic algometer (Somedic Sales AB, Hörby, Sweden) with a probe area of 1 cm^2 was used to assess individual pressure pain thresholds (PPTs) (Kosek et al., 1993). The pressure increased at a rate of approx. 50 kPa/second. Participants were familiarized with the procedure beforehand and instructed to press a response button at their first sensation of pain. PPTs were assessed bilaterally at m. supraspinatus, the lateral epicondyle of the humerus, the gluteal area, and the inside of the knee (these sites correspond to the tender points used in the ACR 1990 classification of FM) (Wolfe et al., 1990). For each individual, we calculated the average PPTs across these 8 sites, as a measure of pressure pain sensitivity (PPT average). For full procedure description, see (Tour et al., 2017).

Assessment of exercise-induced hypoalgesia (EIH)

The maximum voluntary contraction force (MVC) of the right leg

knee extensors (m. quadriceps femoris) was determined as a basis for the assessment of EIH. MVC was tested with a dynamometer (Steve Strong®: Stig Starke HBI, Göteborg, Sweden), with the participant in a fixed sitting position with back support, with hip and knee joints flexed to 90 degrees, legs hanging freely and hands resting in the lap. A non-elastic strap was placed around the ankle and attached to a pressure transducer with an amplifier. Three 5-second measurements of MVC were taken with 1-minute rests in between. The highest of the 3 recorded values was determined to be each participant's MVC. The participants rested for a minimum of 10 min before the EIH session (Larsson et al., 2015).

As we were interested to study global (plurisegmental) effects of EIH, rather than the local (segmental) EIH (Kosek et al., 1996; Lannersten and Kosek, 2010; Kosek and Lundberg, 2003; Rice et al., 2019), we choose to assess PPTs at a resting muscle distant from the contracting m. quadriceps. The EIH was assessed by determining PPTs at the resting left m. deltoideus before (2 baseline values) and during a submaximal isometric contraction of the right knee extensors. The contraction was performed with the Steve Strong®, with participants sitting with their hip and knee joints flexed to 90 degrees. Participants were instructed to perform an isometric knee extension contraction of their right leg and maintain it until they were unable to sustain 30 % of their individual MVC, as indicated by the Steve Strong® (maximum 5 min). PPTs were assessed throughout contraction at the left m. deltoideus every 30 s. Baseline data for all participants in the trial (randomized to exercise and relaxation) regarding PPTs and plurisegmental EIH have been published previously (Tour et al., 2017).

Individual pressure pain calibration for fMRI (P50)

Pressure sensitivity was individually calibrated during visit 2 (i.e., pre-exercise intervention) and 5 (i.e. post exercise intervention). The aim of the calibration procedure was to determine which individual pressure (kPa) that corresponded to a subjective rating of 50/100 mm VAS. Pressure stimulation was delivered at the left thumbnail in FM and HCs using an automated, computer-controlled plastic cylinder with a 1 cm^2 hard rubber probe. First, participants received one ascending series of pressure stimuli (with increasing steps of 50 kPa) in order to determine the pressure pain threshold (PPT, first VAS >0 mm) and stimulation maximum (SM, first VAS >60 mm). Next, within 3 randomized series, 5 different pressure intensities were calculated and delivered within the range of each individual's PPT and SM pressures. In both series, each pressure stimulus was applied for 2.5 s with a 30 s interval. Participants were asked to rate their perceived pain intensity following each stimulus on a VAS ranging from 0 = "no pain" to 100 = "worst imaginable pain". Finally, a polynomial regression function was fitted to the data, using the 15 subjective pain ratings (from the randomized series) to ultimately determine each individual representation of 50 mm VAS (designated as P50). For further information on the calibration procedure (Jensen et al., 2009; Sandström et al., 2019).

Functional magnetic resonance imaging

Participants were scanned during visit 3 (pre-exercise intervention) and visit 6 (post– exercise intervention). MR images were acquired with a 3T General Electric 750 MR scanner installed at the MR Research Center, Karolinska Institutet, Karolinska University Hospital, Stockholm, using a 32-channel head coil. Anatomical MR scans were acquired in both cohorts with a high-resolution BRAVO 3D T1-weighted image sequence (1x1x1 mm^3 voxel size). Functional images covering the whole brain were acquired using a T2*-weighted single-shot gradient echo planar imaging sequence, interleaved axial slice acquisition, number of slices = 56, slice thickness = 3 mm. Flip angle = 90°, 96×96 matrix size, field of view (FOV) = 288×288mm, time repetition/time echo (TR/TE) = 3000/30 ms. Finally, anatomical T2-wieghted scans were collected and screened by a neuro-radiologist for clinical abnormalities.

Following the collection of anatomical MR scans, participants underwent a pressure probe stimulation paradigm using the computer-controlled plastic pressure stimulator (described above) while functional MR images were collected. Participants were stimulated with their previous individually calibrated painful pressure (P50) and a fixed non-painful pressure (50 kPa) over their left thumbnail. Using the identical methodology, we have previously shown that the thumbnail serves as a reliable stimulation site for healthy participants (Jensen et al., 2009) and FM patients (Jensen et al., 2009; Sandström et al., 2019). Participants underwent two runs of pressure stimulations. Each run consisted of 30 pressure stimuli (15 painful and 15 non-painful). All pressures were delivered for 2.5 s each, in a pseudo-randomized order, jittered over time. Mean interval between onsets of stimuli of 15 s (range 10–20 s). Total duration of each run was 8 min and 15 s. At the end of the MR session, resting state data was collected in both cohorts (published elsewhere, *see* (Flodin et al., 2014).

Exercise intervention

The interventions have previously been described in detail (Larsson et al., 2015). Here we only present the resistance exercise, as no date related to the relaxation exercise are presented in the current article. The 15-week resistance exercise program was performed twice a week under supervision from experienced physiotherapists. Before the participants started the intervention, they had an individual introductory meeting with a physiotherapist. At this meeting, the physiotherapist provided individual instructions and adjustments of each exercise according to the individuals' condition, including a test of their 1 repetition maximum (1RM) and tolerance before deciding on the initial load of each exercise. Each session of the exercise program lasted for about 60 min, including 10 min warm-up by ergometer cycling, isometric exercises for the deep muscles in the back and stomach, and concentric and non-concentric exercises for the legs, back, stomach, arms and hands. The program ended with stretching exercises (Larsson et al., 2015).

Participants' individual 1RMs for the different exercises were tested before starting and at 3 time points during the program. The initial exercise loads were set at approximately 40 % of 1RM. The initial exercise training was made up of 2 sets with 15 to 20 repetitions within the individual symptom tolerance with a 45 s rest between each set. The load was progressively raised. After 8 weeks, the load reached up to 70 % to 80 % of 1RM with 2 sets of 8 to 10 or 5 to 8 repetitions, respectively. The body weight was used as load for the back and stomach, which was raised by adding more lever arm. At week 5 and 8, leg exercises for explosive strength were also included (Larsson et al., 2015).

Statistics

Descriptive data are presented as median (25th to 75th percentiles). Differences within groups were calculated with the Wilcoxon signed ranked test and between group differences with the independent samples Mann-Whitney U Test.

Given the large interindividual differences in pressure pain sensitivity even among healthy participants (Sandström et al., 2019), we chose to compare the relative effects of exercise on PPTs, in accordance with our previous studies (Lannersten and Kosek, 2010; Tour et al., 2017). To control for individual variation with regard to baseline PPT values, EIH scores were calculated for each individual as the PPT value at the end of contraction minus the first PPT value at baseline, divided by the first PPT value at baseline (Tour et al., 2017; Lindstedt et al., 2011). Positive values indicate pain inhibition, while negative values indicate pain facilitation. The statistical analyses of average PPTs, P50 and the EIH score, respectively, were performed using a repeated measures ANOVA with the within-subject factor INTERVENTION (before and following exercise intervention) and the between-subject factor GROUP (FM patients and controls). Greenhouse-Geisser corrections were used in cases of a significant test of sphericity. The analyses were performed using SPSS software, version 26.

Functional magnetic resonance imaging analysis

Imaging data analyses were performed using the Statistical Parametric Mapping 12 (SPM12) software (Friston et al., 1997) (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/); running under Matlab (The MathWorks, Natick, MA, version R2019a). Prior to preprocessing, scans were quality-checked and reoriented to the anterior/posterior commissure line to improve the co-registration and normalization process. Functional images were spatially realigned using a six-parameter affine transformation and registered to the mean. Functional and structural images were co-registered and normalized to Montreal Neurological Institute (MNI) space. An 8 mm full-width-half-maximum (FWHM) Gaussian kernel was used for spatial smoothing of images. Frame-wise displacement (FD) was used to assess head motion from one volume to the next, converting rotational displacements (sum of the absolute values of the derivatives of the six realignment parameters) from degrees to millimeters by calculating displacement on a sphere with a 50 mm radius. Excessive head motion was considered for images exceeding FD >0.5, in >15 % of the images in both runs of pressure stimulation in either pre- or post-intervention scanning sessions. None of the participants exhibited excessive movement in both runs of pressure stimulation in either pre- or post-intervention scans, and thus none were excluded. However, 2 participants exhibited excessive head motion for the second but not first run of pressure stimulation during the post-intervention scanning session.

1st level general linear model (GLM) included regressors of interest convolved with the canonical hemodynamic response function for stimulus intensity (i.e., pain and sensory) during pre- and post-exercise intervention sessions. Six motion parameters were added as regressors of no interest.

2nd level paired *t*-test was used to investigate the main effects of pain-related brain activation pre- vs post-exercise intervention across all fMRI participants, as well as within-group differences in pain-related brain activation pre- vs post-intervention. Full factorial design was used to assess interactions between [group × time]; that is, group differences in either pain- or sensory-related brain activation pre- vs post-exercise intervention.

Statistical significance for all analyses (including BOLD and functional connectivity) was considered for clusters surviving whole-brain family-wise error (FWE) correction for multiple comparisons $P_{FWE} < 0.05$, at an initial cluster-forming threshold of $p < 0.001$ with at least 20 contiguously activated voxels. Age was included as a covariate of no interest across all analyses. MNI stereotactic atlas coordinates [x, y, z] were used to localize cluster brain activation and labelled through the Automated Anatomical Labeling (AAL) digital atlas in MRIcron.

Psychophysiological interaction analysis

In order to further investigate the effects of exercise on cerebral pain processing, a secondary psychophysiological interaction (PPI) analysis (Bostan and Strick, 2018) was performed. A PPI analysis is a connectivity model which can be used to investigate the interaction between an experimental condition (psychological parameter: in this context, applied pressure stimuli) and a predetermined source region or a volume of interest (VOI) (physiological parameter: i.e. the BOLD fMRI signal time series). A PPI analysis does not convey information about directionalities in connectivity between brain regions.

Two secondary VOI-to-whole brain PPI task-based functional connectivity analyses were performed based on our univariate fMRI BOLD results that revealed a statistical significant main effect of exercise intervention across all fMRI participants for contrast [Pain(post > pre)]). Specifically, an 8-mm-diameter spherical VOI was defined in the left caudate [MNI −10 22–2] and an 8-mm-diameter diameter spherical VOI was defined in left superior frontal gyrus/dorsolateral prefrontal cortex (dlPFC) [MNI –22 32 36]. Our choice of establishing functional connectivity from these two regions is supported by previous literature underscoring the role of cortico-striatal-cerebellar connectivity in sensorimotor functioning and motor adaptation (Bostan and Strick, 2018; Galea et al., 2015).

Results

Symptoms

Descriptive data are presented in Table 2. Compared to HC, FM patients had higher ratings of pain (VAS) as well as depression/anxiety (HADS) at baseline and following the exercise intervention (all $p < 0.002$). Statistically significant improvements were seen in the FM EIH cohort after the exercise intervention regarding current pain intensity (VAS) ($p = 0.001$), impact of fibromyalgia (FIQ) ($p = 0.002$) and depression (HADS-D) ($p = 0.010$). In the FM fMRI cohort, a significant decrease in FIQ scores was seen following the intervention ($p = 0.025$), indicating reduced impact of disease. No statistically significant changes were seen in the two healthy cohorts (HC EIH and HC fMRI). No statistically significant differences were found between the exercise intervention cohort and the fMRI subsample at baseline or following the intervention.

Pressure pain thresholds

There was a significant GROUP effect ($df = 1$; $F = 89.7$; $p < 0.0001$), but no significant effect for INTERVENTION ($df = 1$; $F = 1.15$; $p = 0.28$) or significant GROUP × INTERVENTION interaction ($df = 1$; $F = 2.48$; $p = 0.12$), meaning that FM patients had lower PPTs than HC, but the exercise intervention did not affect PPTs in either group (Fig. 2A).

Exercise-induced hypoalgesia

Regarding EIH, there was a significant GROUP effect ($df = 1$; $F = 7.64$; $p = 0.007$), but no effect for INTERVENTION ($df = 1$; $F = 0.12$; $p = 0.73$) or significant GROUP × INTERVENTION interaction ($df = 1$; $F = 0.49$; $p = 0.49$). Hence, the results showed that EIH was dysfunctional in FM, but the exercise intervention had no effect on EIH in either group (Fig. 2B).

Suprathreshold pressure pain (P50)

There was a significant GROUP effect ($df = 1$; $F = 14.3$; $p = 0.001$) and a significant effect for INTERVENTION ($df = 1$; $F = 12.8$; $p = 0.001$), but no significant GROUP × INTERVENTION interaction ($df = 1$; $F = 0.21$; $p = 0.65$). FM patients had lower P50 than controls, and post hoc analysis revealed a significant increase in P50 following the exercise intervention in FM patients ($p = 0.001$), although the change was not statistically significant in HC ($p = 0.11$) (Fig. 3B).

Cerebral pain processing (fMRI)

In the fMRI subgroup, there was a significant main effect of exercise on pain-related (P50) brain activation across all participants ($n = 37$). Specifically, all the fMRI participants exhibited increased pain-related brain activation post- vs pre-intervention while painfully stimulated over the left thumbnail (i.e. contrast all fMRI participants[pain(post > pre)]) in left caudate and the left superior/midfrontal gyrus (dlPFC) (Table 3, Fig. 3A). These results survived even when the analysis was performed using the increase in P50 (post-pre) as a covariate of no interest. No effect of exercise was observed across all participants post- vs pre-intervention when participants were stimulated with a sensory (50 kPa) pressure over their left thumbnails. No statistically significant within- or between-group differences were seen in pain-related or sensory-related brain activation post- vs pre- or pre- vs post-exercise intervention.

Table 2
Subject characterization. EIH = Exercise-Induced Hypoalgesia, fMRI = functional Magnetic Resonance Imaging, FM = fibromyalgia patients, HC = healthy controls, VAS Pain = Pain intensity ratings using 100 mm Visual Analogue Scale, FIQ total = Fibromyalgia Impact Questionnaire total score, HADS = Hospital Anxiety and Depression Scale, D = depression, A = Anxiety.

Cohort	Questionnaire		Before exercise intervention	After exercise intervention	Within-group diff p-value	Group diff p-value
EIH cohort	**Pain VAS** (median, 25–75 %)	FM	54.0 (33.7–70.2)	31.0 (21.5–58.0)	0.001	Baseline 0.001
		HC	0 (0–0)	0 (0–0)	N.A.	Post test 0.001
	FIQ total (median, 25–75 %)	FM	59.8 (50.1–73.6)	56.2 (44.3–68.7)	0.002	N.A.
		HC	N.A.	N.A.	N.A.	N.A.
	HADS-D (median, 25–75 %	FM	7.0 (5.0–8.2)	5.0 (2.5–9.0)	0.010	Baseline 0.001
		HC	1.5 (0–3.2)	1.0 (0–3.0)	0.402	Post test 0.001
	HADS-A (median, 25–75 %)	FM	8.0 (4.0–11.0)	7.0 (3.0–12.0)	0.522	Baseline 0.001
		HC	3.0 (1.0–4.2)	2.0 (1.0–5.0)	0.254	Post test 0.001
fMRI subsample	**VAS pain** (median, 25–75 %)	FM	38.0 (28.5–54.8)	37.5 (26.2–54.5)	0.239	Baseline 0.001
		HC	0 (0–0)	0 (0–0)	N.A.	Post test 0.001
	FIQ total (median, 25–75 %)	FM	63.9 (52.8–73.8)	55.4 (45.3–70.4)	0.025	N.A.
		HC	N.A.	N.A.	N.A.	N.A.
	HADS-D (median, 25–75 %)	FM	6.5 (5.0–10.2)	7.0 (3.2–10.0)	0.169	Baseline 0.001
		HC	2.0 (0–4.0)	1.0 (1.0–5.0)	0.796	Post test 0.001
	HADS-A (median, 25–75 %)	FM	9.0 (6.2–10.0)	7.5 (3.0–12.0)	0.408	Baseline 0.001
		HC	2.0 (0–4.0)	2.0 (1.0–6.0)	0.873	Post test 0.002

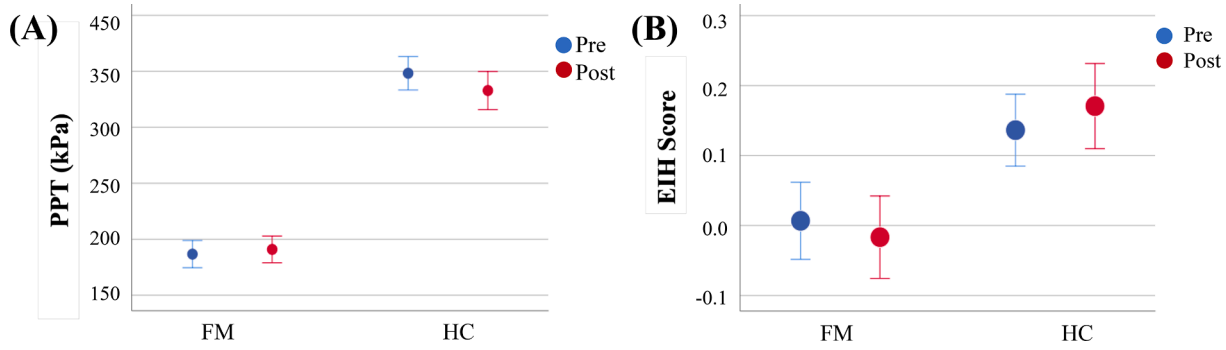

Fig. 2. (A) Illustrate mean (±1 SEM) pressure pain thresholds (PPTs) (kPa) pre (blue dots) and post (red dots) exercise intervention. Fibromyalgia (FM) patients had lower PPTs compared to healthy controls (HC) ($p < 0.0001$), but no change was seen following the exercise intervention in either group. (B) Illustrate mean (±1 SEM) exercise-induced hypoalgesia (EIH) score before (blue dots) and after (red dots) the exercise intervention. FM patients had a reduced function of EIH compared to HC ($p = 0.007$). No change in EIH was seen following the exercise intervention in either group. SEM = standard error of the mean, kPa = kilopascal.

Psychophysiological interaction (PPI)

Across all fMRI participants [pain(post > pre)], using the left caudate [MNI −10 22–2] as a seed region, a significant interaction was established in a cluster located within the left inferior occipital lobe, extending to fusiform gyrus on the border of cerebellum (Table 3). Within the FM group [pain(post > pre)], a significant PPI interaction occurred between the left caudate and left occipital lobe, extending to the border of cerebellum (Table 3, Fig. 4). No significant PPI interaction was found within HC [pain(post > pre)] when using a VOI positioned in the left caudate. No significant PPI interaction was found in either of the two groups (nor collapsed groups) when using a VOI positioned in the left dlPFC.

Discussion

To our knowledge, this is the first study of the effect of a long-term physical exercise intervention in FM on descending pain modulation and cerebral pain processing. In line with the European treatment guidelines recommending physical exercise for FM (Macfarlane et al., 2017), we found beneficial effects of the exercise intervention on a variety of FM symptoms (Larsson et al., 2015; Palstam et al., 2014; Palstam et al., 2016; Larsson et al., 2017; Larsson et al., 2018; Martinsen et al., 2018) reflected here as reduced pain intensity and lower FM severity in the present EIH cohort. However, EIH remained unaltered and dysfunctional in FM patients following the 15 weeks of resistance exercise. Regarding brain imaging data, a significant main effect of exercise on pain-related brain activation was established across all fMRI participants within the left dlPFC and left caudate. Increased pain-related functional connectivity was seen between regions within the striatal-occipital loop post- compared to pre-exercise intervention in FM patients. The current results suggest that the physical exercise intervention affected pain-related processing within intra-cerebral cortico-striatal-occipital brain networks, rather than strengthening the descending pain inhibitory pathways.

The effect of exercise intervention on exercise-induced hypoalgesia

As expected, FM patients had significantly lower PPTs and less functional EIH compared to HC at baseline, which is in accordance with previous studies (Kosek et al., 1996; Lannersten and Kosek, 2010). However, contrary to our hypothesis, the exercise intervention failed to reduce pain sensitivity (increase PPTs) or improve EIH in FM patients. To our knowledge, effects of exercise on EIH have not previously been assessed in a patient group with an established EIH dysfunction. Our results tally with previous clinical studies showing that neuromuscular exercise for an average duration of 3 months did not affect PPTs or EIH in patients with painful osteoarthritis of the hip or knee, although it must be acknowledged that the baseline function of EIH was normal in these patients (Kosek et al., 2013). Also, a previous study reported no change in PPTs or EIH in patients with rheumatoid arthritis following a long-term (2-year) period of health-enhancing physical activity (Löfgren

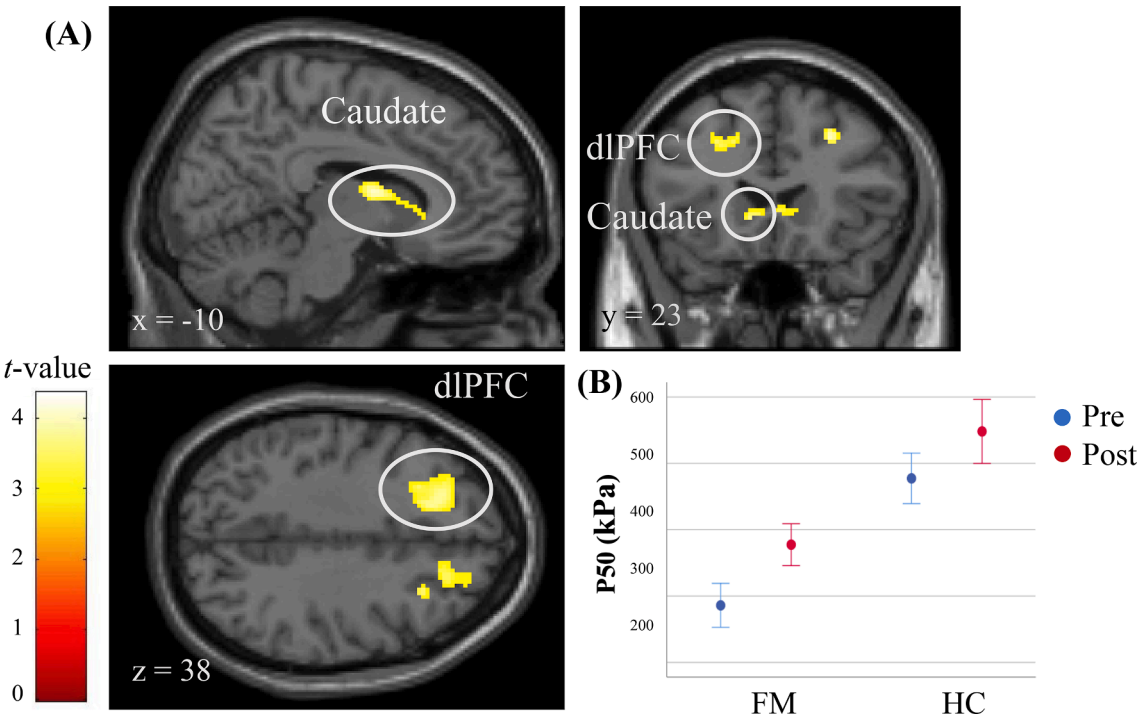

Fig. 3. A) Depicts main effect of exercise intervention on pain-related BOLD brain activation for all fMRI participants during P50 painful stimulation (i.e. ALL[Pain (post > pre)]. Specifically, following compared to prior to exercise intervention, all participants increased brain activation in response to painful pressure in left caudate and left superior/midfrontal gyrus (also known as dorsolateral prefrontal cortex, dlPFC). Color scale represents *t*-values. B) Illustrate mean (±1 SEM) P50 before (blue dots) and after (red dots) exercise intervention. FM patients had significantly lower P50 than controls ($p = 0.001$) and P50 increased following the intervention in both groups ($p = 0.001$). No significant interaction was found between the increase in P50 and the post > pre changes in pain-related BOLD brain activation. The BOLD activation maps are derived at an initial threshold of < 0.001 uncorrected, with 20 contiguously activated voxels. Clusters surviving FWE < 0.05 are indicated with gray circles. BOLD = blood-oxygen-level-dependent; P50 = pain intensity of ~ 50 mm on a 100 mm visual analogue scale; FM = fibromyalgia.

Table 3
Activated brain regions and functional connectivity during experimentally evoked painful pressure. dlPFC = dorsolateral prefrontal cortex; MNI = Montreal Neurological Institute × y z coordinates; FM = fibromyalgia patients; HC = healthy controls; L = left; R = right; n/s = non significant.

Blood Oxygen Level Dependant							
All Subjects Pain [Pre > Post]	**x**	**y**	**z**	**k/E**	***t*-value**	***z*-score**	**FWE**
n/s							
All Subjects Pain [Post > Pre]	**x**	**y**	**z**	**k/E**	***t*-value**	***z*-score**	**FWE**
L Caudate	−10	22	−2	337	4.04	3.64	0.049
L superior frontal gyrus/midfrontal gyrus (dlPFC)	–22	32	36	351	4.35	3.87	0.044
All Subjects Sensory [Pre > Post]	**x**	**y**	**z**	**k/E**	***t*-value**	***z*-score**	**FWE**
n/s							
All Subjects Sensory [Post > Pre]	**x**	**y**	**z**	**k/E**	***t*-value**	***z*-score**	**FWE**
n/s							
Psychophysiological Interaction							
L Caudate [MNI −10 22–2]							
All Subjects Caudate Pain [Post > Pre]	**x**	**y**	**z**	**k/E**	***t*-value**	***z*-score**	**FWE**
L inferior Occipital lobe	−40	−70	−10	381	4.95	4.59	0.023
FM Caudate Pain [Post > Pre]	**x**	**y**	**z**	**k/E**	***t*-value**	***z*-score**	**FWE**
L inferior occipital lobe	−40	−70	−10	1982	5.13	4.40	0.001
HC Caudate Pain [Post > Pre]	**x**	**y**	**z**	**k/E**	***t*-value**	***z*-score**	**FWE**
n/s							
L dlPFC [MNI –22 32 36]							
All Subjects dlPFC Pain [Post > Pre]	**x**	**y**	**z**	**k/E**	***t*-value**	***z*-score**	**FWE**
n/s							
FM dlPFC Pain [Post > Pre]	**x**	**y**	**z**	**k/E**	***t*-value**	***z*-score**	**FWE**
n/s							
HC dlPFC Pain [Post > Pre]	**x**	**y**	**z**	**k/E**	***t*-value**	***z*-score**	**FWE**
n/s							

et al., 2018a) however these patients also had normal EIH at baseline (Löfgren et al., 2018b). Notably, we found no effect on PPTs or EIH in our HC that completed the same exercise intervention as our FM patients.

Although, our results indicate that the pain-relieving effects of exercise in chronic pain patients depend on other mechanisms than improving EIH, it must be remembered that EIH assessments typically rely on single bouts of aerobic or resistance exercise (Rice et al., 2019;

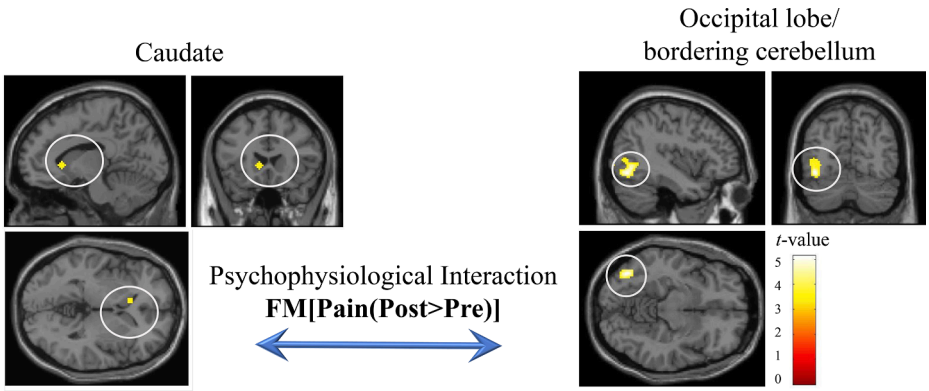

Fig. 4. Psychophysiological interaction (PPI) connectivity analysis revealed statistically significantly increased functional connectivity within FM patients only when patients were painfully stimulated following compared to prior to exercise intervention (i.e. FM[Pain Post > Pre]). The increase in functional connectivity was between caudate and occipital lobe, on the border to cerebellum. Color scale represents *t*-values.

Vaegter and Jones, 2020) and thus may not reflect other pain-relieving mechanisms of long-term, recurrent physical exercise. In fact, there is evidence that long-term regular exercise may reduce pain sensitivity and improve endogenous pain inhibitory mechanisms such as conditioned pain modulation (CPM) in healthy subjects as well as chronic pain patients (Vaegter and Jones, 2020). Hypothetically, such mechanisms could contribute to the reduced pain intensity reported by our FM patients following the 15-week exercise intervention. However, peripheral mechanisms could also be of importance, as supported by our previously published results demonstrating an association between reduced intramuscular concentrations of pyruvate and glutamate and reduced pain intensity following the exercise intervention in FM patients (Gerdle et al., 2016).

The effect of exercise intervention on cerebral pain processing

Following exercise intervention, both groups increased brain activation in left dorsolateral prefrontal cortex (dlPFC) and left caudate when painfully stimulated over the left thumbnail (Table 3 and Fig. 3). Although the fronto-striatal pain-related brain activation was indeed present bilaterally, both of the cluster *peaks* of activation were located ipsilateral to the stimulation site. The reason for the ipsilateral peaks can be explained by the subtraction of brain activation prior to exercise intervention, from the brain activation following exercise intervention. That is, most of the brain activation contralateral to the stimulation site, was already present prior to the exercise intervention, but got subtracted from the contrast of [Post minus Pre].

The dlPFC is involved in descending pain modulation, cognitive aspects of the pain experience and regarded as a key region for initiating placebo-related changes in pain perception (Seminowicz and Moayedi, 2017). The caudate nucleus is a striatal dopamine-rich structure involved in motor processing, spatial working memory (Seminowicz and Moayedi, 2017) and evaluation of reward and salience (Haber, 2016). Together, the caudate nucleus and the prefrontal cortex (PFC) form the dopaminergic fronto-striatal loop, associated with motivation and movement, in which the PFC executes top-down control over motor performance (Doyon et al., 2009; Hardwick et al., 2013; Gilat et al., 2017). Thus, both structures are essential for the regulation of complex, goal-directed behaviors (Haber, 2016). With respect to pain, explicit self-regulation of pain during different intensities of heat pain stimuli has been associated with changes in functional connectivity between ventromedial PFC and striatal structures, mainly nucleus accumbens (NAcc), but also the caudate (Woo et al., 2015). Moreover, decreased NAcc/caudate gray matter volume (Baliki et al., 2012) as well as increased functional connectivity between mPFC and striatal regions have been reported to predict the transition from an acute to a chronic back pain state (Baliki et al., 2012; Hashmi et al., 2013). In this perspective, caudate activation was associated with spontaneous fluctuations of back pain intensity in individuals with subacute, but not chronic, low back pain, indicating that reduced activation was involved in the development of the aberrant cerebral pain processing seen in the chronic low back pain cohort (Hashmi et al., 2013). Taken together, the current results add to the longitudinal pain literature, suggesting that a 15-week exercise intervention affects fronto-striatal brain activity during painful pressure stimulation in FM patients and HC alike. These observations are likely related to refined motor performance and motor control, albeit during pressure pain stimulation, but could hypothetically also be related to cerebral pain modulation.

The current results show that the subjectively calibrated P50 pressure (which was used during the fMRI scan) increased following the exercise intervention, meaning that a higher absolute pressure was needed to elicit pain rated as 50/100 on a VAS. The P50 is a robust measure not susceptible to change over time (Jensen et al., 2012a; Jensen et al., 2014). Therefore, the increase in P50 indicates reduced sensitivity to suprathereshold pain following the exercise intervention, while no effect was seen on pain thresholds (PPTs). Our results are in accordance with a previous study, demonstrating reduced sensitivity to suprathreshold but not threshold pain in physically active women (Ellingson et al., 2012).

Further, the fMRI findings remained unaltered when corrected for the increase in P50. One interpretation is that the exercise induced changes in fronto-striatal brain activity were unrelated to pain modulation. An alternative interpretation is that the pain-related functional alterations in FM patients and HC were not merely a result of the increased P50 stimulation (in kPa) following treatment.

Task-based functional connectivity following exercise intervention

The increased brain activation in the left caudate and left dlPFC were further investigated through PPI functional connectivity analysis. Across all fMRI participants, the left caudate revealed a significantly increased interaction with the left occipital lobe, extending to the border of cerebellum, during painful stimulation over the left thumbnail post- vs pre-exercise intervention. The increment in task-based functional connectivity seemed to be driven by FM patients, as no task-based connectivity was found for the left caudate within the HC group. A *meta*-analysis comprising 20 exercise intervention-based fMRI studies, revealed in two separate sub-analyses, that shorter duration of the exercise interventions ($\leq$12 weeks) or inactive participants at baseline are most likely to acquire primary peak changes in the occipital and limbic lobe following exercise intervention (Yu et al., 2021). These changes may be related to increments in perceptual abilities and motion cognition (Yu et al., 2021). Further, as mentioned, the current occipital cluster was extending to the border of cerebellum, which is highly interconnected with the

basal ganglia are interconnected at the subcortical level through dense di-synaptic projections. It has been suggested that motivation-related (reward-/error-based feedback) signals from the basal ganglia drive the cerebellum to optimize movement and adjust action choices (Bostan and Strick, 2018; Galea et al., 2015).

Treatment effects on cerebral pain processing in FM

Taken together, the current results show that a 15-week resistance exercise intervention reduced pain and FM symptoms, without directly influencing the dysfunctional EIH. Brain imaging data revealed functional alterations following exercise intervention, where FM patients exhibited increased cortico-striatal brain activation during evoked pain, in combination with increased pain-related functional connectivity within the cortico-striatal-occipital loop. The current results indicate possible restoration of abnormalities or improvement within this network, which would hypothetically influence restoration of motor control, cognition and perception carried out by this network (Bostan and Strick, 2018; Yu et al., 2021) and partially explain the increased P50 pressure pain tolerance in FM patients.

The fact that we have used the same evoked pain fMRI methodology to assess the effects of different treatments in FM allows for analysis of differences and similarities regarding cerebral pain modulation. When comparing exercise with the effects following either 12 weeks of drug treatment with milnacipran (Jensen et al., 2014), a serotonin noradrenaline reuptake inhibitor (SNRI) or acceptance commitment therapy (ACT) (Jensen et al., 2012b), respectively, different patterns of treatment related changes emerge. An increase in P50 was seen following exercise and in responders to SNRI treatment (Jensen et al., 2014), but not following ACT (Jensen et al., 2012b). In addition, while pain-related activation was increased in the dlPFC and caudate following exercise (the cortico-striatal-occipital loop), increased activation of posterior cingulate cortex (PCC) and precuneus was observed in milnacipran responders suggesting involvement of the default mode network (Jensen et al., 2014), and increased activation of vlPFC and orbitofrontal cortex following ACT, suggesting an impact on cognitive control (Jensen et al., 2012b). Furthermore, increased pain-related functional connectivity was seen between the vlPFC and thalamus (a basal-ganglia-associated brain region) (Jensen et al., 2012b) suggesting partially similar effects of mind (ACT) and body (exercise) interventions on cerebral pain-related processing, with both exerting their effects on cortico-striatal/cortico-thalamic loops. The current findings indicate that the beneficial effects of exercise, SNRIs and CBT interventions in FM are partially mediated by different cerebral or peripheral mechanisms, and thus support the clinical practice of combining treatments in order to optimize the response.

Limitations

The current study lacks a non-exercising control group, which hinders us from controlling for time-related effects on pressure pain response. However, our previous studies using the very same method indicate that P50 normally remains stable over time (Jensen et al., 2012a; Jensen et al., 2014). The current fMRI results were corrected for multiple comparisons ($P_{FWE} = 0.05$ on an initial cluster-forming threshold of $p < 0.001$ uncorrected), yet the relatively small sample size of the fMRI cohort (FM $n = 18$; HC $n = 19$) implies that the brain imaging results should be interpreted with caution and need to be reproduced in a larger cohort. Finally, all participants in the current study volunteered to participate in a randomized exercise/relaxation study. Hence, the patient recruitment may be biased towards less severely affected FM patients and may not be generalizable to more severely affected patients with FM.

Conclusions

The fifteen-week resistance exercise intervention reduced pain and FM symptoms, but EIH dysfunction remained unaltered in FM patients. In fact, neither patients nor HC revealed any improvements in EIH following exercise intervention. Brain imaging data indicated a significant main effect of exercise on pain-related brain activation across all fMRI participants within the left dlPFC and left caudate and increased pain-related functional connectivity was observed between striatum and occipital lobe/cerebellum within FM patients. Taken together, the current results suggest that physical exercise functionally alter pain-related cerebral processing within cortico-striatal-occipital loop, rather than strengthening the descending pain inhibitory pathways, per se.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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