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Normalization of aberrant resting state functional connectivity in fibromyalgia patients following a three month physical exercise therapy

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ABSTRACT

Physical exercise is one of the most efficient interventions to mitigate chronic pain symptoms in fibromyalgia (FM). However, little is known about the neurophysiological mechanisms mediating these effects. In this study we investigated resting-state connectivity using functional magnetic resonance imaging (fMRI) before and after a 15 week standardized exercise program supervised by physical therapists. Our aim was to gain an understanding of how physical exercise influences previously shown aberrant patterns of intrinsic brain activity in FM. Fourteen FM patients and eleven healthy controls successfully completed the physical exercise treatment. We investigated post- versus pre-treatment changes of brain connectivity, as well as changes in clinical symptoms in the patient group. FM patients reported improvements in symptom severity. Although several brain regions showed a treatment-related change in connectivity, only the connectivity between the right anterior insula and the left primary sensorimotor area was significantly more affected by the physical exercise among the fibromyalgia patients compared to healthy controls. Our results suggest that previously observed aberrant intrinsic brain connectivity patterns in FM are partly normalized by the physical exercise therapy. However, none of the observed normalizations in intrinsic brain connectivity were significantly correlated with symptom changes. Further studies conducted in larger cohorts are warranted to investigate the precise relationship between improvements in fibromyalgia symptoms and changes in intrinsic brain activity.

1. Introduction

Fibromyalgia (FM) is a condition characterized by widespread chronic pain and is often accompanied by cognitive dysfunction and fatigue. The pathogenesis is still largely unknown, but there is evidence of both peripheral and central pathophysiology (for a review, see Clauw, 2014). The diagnosis is currently based on self-reported pain, and as of yet, no laboratory test can directly test for FM. Intriguingly however, several brain imaging studies of FM patients indicate an altered functional brain structure which is related to aberrant pain evoked brain activation, particularly in the anterior cingulate cortex and thalamus (Jensen et al., 2013). Resting state brain connectivity constitutes a promising complement to the traditional task-based fMRI studies employing subtraction designs that disregard the brain activity reflecting sustained pain states. Resting state fMRI studies have reported altered intrinsic brain activity in FM patients including: decreased connectivity between insula and prefrontal areas (Ichesco et al., 2014) and the periaqueductal grey (PAG) (Pujol et al., 2014), increased connectivity between insula and medial regions of the default mode network (DMN) (Napadow et al., 2010), and decreased connectivity between somatosensory regions and visual and auditory cortices (Pujol et al., 2014). Using a comprehensive set of analytical approaches to characterize intrinsic brain activity in FM, we recently showed a decreased connectivity between pain-related and sensorimotor brain areas during rest (Flodin et al., 2014).

Physical exercise is a potent treatment for FM, on par with the efficiency of cognitive behavioural therapy, education in coping strategies and pharmacological interventions (Clauw, 2014). In this study, we aimed to investigate if physical exercise could normalize the previously described aberrant patterns of intrinsic brain connectivity in FM and if this was related to symptom improvement. To our knowledge, this is the first study to investigate the longitudinal effects of physical exercise

Abbreviations: FM, fibromyalgia; PAG, periaqueductal grey; FIQ, Fibromyalgia Impact Questionnaire; SF36BP, bodily pain subscale of the Short Form Health Survey.

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on intrinsic brain activity in FM. Our hypothesis was that the physical training program would influence the previously detected deviant connectivity patterns in six pairs of brain ROI-to-ROI (Region-of-Interest) connectivity in FM patients (Flodin et al., 2014). We further aimed to investigate the extent to which longitudinal changes in connectivity correlated with changes in symptoms.

2. Methods

2.1. Subjects

Subject recruitment and inclusion criteria were identical to our baseline study (Flodin et al., 2014). All FM patients satisfied the American College of Rheumatology (ACR) 1990 disease criteria for FM. Of the 16 female subjects included in the baseline study, two subjects failed to comply with the longitudinal study protocol. The mean age of the remaining fourteen subjects was 48.4 (range 25–64) years (all female). The mean symptom gravity (assessed with the Fibromyalgia Impact Questionnaire (FIQ), see Bennett, 2005 for reference) was 60.8 ($SD =$ 11.8), and the mean FM duration was 7.3 years ($SD = 4.0$). Among the 22 female subjects originally included as healthy controls in the baseline study, nine subjects were only scanned once, fMRI data from one subject was discarded due to excessive head-motion, and fMRI data from one subject was rejected due to technical failures in the image acquisition process. Thus, fMRI resting-state data from eleven healthy controls were included (mean age 41.8 years, range 20–63).

2.2. Training intervention

A 15-week exercise program with two sessions each week was carried out under supervision from a physiotherapist (PT). Before the participants started the intervention, they had individual meetings with a PT who tested their one repetition maximum (1 RM) and tolerance before deciding the initial load of each exercise. At the same time the participants received individual instructions for each exercise. Each session lasted for about 1 h and included 10 min of warming 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.

The participants' individual 1 RM for the different exercises were tested before starting and at three time points during the program. For the legs and arms the initial loads were set at approximately 40% of one 1 RM and the participants were instructed to repeat each exercise 15–20 times in one to three sets within symptom tolerance. In between each set, the participants rested for at least 45 s. After 5 weeks the load was raised up to about 50% of 1 RM with 2 sets of 12–15 repetitions, after 8 weeks up to about 60% of 1 RM with 2 sets of 10–12 repetitions and after 12 weeks up to about 70% of 1 RM with 2 sets of 8–10 repetitions. Leg exercises for explosive strength were also included at weeks five and eight.

The participants reported pain and other adverse effects of the exercise program to the PT during every session. In the case that the level of pain increased without returning back to normal within a few days, the participants were instructed to lower the load, but continue to do the exercise. The same instructions were given if the participants had a bad day or an increase of symptoms. If any special exercise was causing problems the participants were instructed to refrain from doing it. The PT followed up on program compliance; if participants did not participate in a session they were instructed to give notice with the reason of absence, on which the physiotherapist made a follow-up phone call. The overall compliance rate was high, with an average of 29.12 ($SD =$ 3.2) training sessions taken for the 25 participants (for FM: $M = 29.4$, $SD = 1.6$; HC: $M = 28.7$, $SD = 4.5$). There was no significant group difference with regard to compliance ($t(23) = 0.52$, $p = .60$).

2.3. Behavioural measures

We used two behavioural measures to estimate pain and fibromyalgia symptomatology. We used the bodily pain subscale of the Short Form Health Survey (SF36BP) for pain assessment, since this assesses pain during a 4 week period and thus reflects long-term changes, disregarding temporary fluctuations in pain intensity (Contopoulos-Ionannidis et al., 2009). In addition, we used the Fibromyalgia Impact Questionnaire (FIQ), which is a general questionnaire regarding the impact of fibromyalgia on everyday life (Bennett, 2005).

2.4. MRI data acquisition

Anatomical and functional MR imaging were performed on a 3 T General Electric 750 MR scanner. For each subject we performed one resting state scan consisting of 200 volumes, using an echo-planar imaging sequence with TR/TE = 2500/30 ms, flip = 90°, 49 slices, 96 × 96 matrix size, FOV = 288×288 mm, slice thickness = 3 mm using interleaved slice acquisition. In the resting state condition, subjects were instructed to lie still and rest, and keep their eyes closed and try not to fall asleep. Prior to the resting state fMRI data acquisition, subjects underwent two fMRI sessions of a task-evoked pain fMRI paradigm (approx. 7 min each), and two sessions of an fMRI adopted version of the Stroop task (approx. 7 min each). Data from the task-evoked fMRI sessions will be reported elsewhere.

2.5. Resting state fMRI data analysis

In this study we investigated longitudinal changes (post- versus pre-physical exercise treatment) of functional connectivity of six seed regions located in pain regions as demarked by a metaanalysis on 314 pain studies carried out in the framework of neurosynth (Yarkoni et al., 2011), that we previously found to be affected by FM in our baseline study (FM: n = 16, HC: n = 22, see Flodin et al., 2014). Specifically, the spherical Region-of-Interest (ROI, with a radius of 4 mm) were located in the insula, sensorimotor cortex and thalamus. A detailed list of the anatomical location of the five seed ROIs and the corresponding six target clusters is given in Table 1. Supplementary Fig. S1 illustrates the whole brain connectivity maps pertaining to each of the seed regions shown at baseline for both the FM and the HC cohort.

Image preprocessing, seed-based correlation analysis (SCA) and group-level analyses were carried out in Matlab (Mathworks Inc., Natick, MA, USA). Prior to SCA, imaging data were preprocessed using the Matlab toolbox SPM12 (Wellcome Trust Centre of Neuroimaging, University College London, UK). Image preprocessing included slice time correction to the middle slice, realignment to the mean image using the 4th degree of B-spline interpolation, co-registration of functional and structural images, tissue segmentation of structural images, normalization of structural and functional scans to the MNI template using the deformation field obtained from the segmentation (4th degree B-spline function, resampling to 2 mm isotropic voxels). Finally, functional volumes were spatially smoothed using an 8 mm FWHM Gaussian kernel. Subject level SCA analyses were carried out using the Conn toolbox (http://www.nitrc.org/projects/conn) (Whitfield-Gabrieli & Nieto-Castanon, 2012). Functional volumes were band pass filtered at 0.008–0.09 Hz (default values). Subject specific nuisance regressors included 6 movement and their time derivatives, and 5 regressors pertaining to white matter and CSF signals respectively, using a component based noise correction (CompCor) approach (Behzadi et al., 2007). Additionally, images that were regarded as movement outliers were regressed out. Outliers were detected using the ART toolbox (http://nitrc.org/projects/artifact_detect/) and defined as volumes with frame wise displacement (FD) larger than 0.5 mm or signal intensity changes greater than 3 standard deviations (default thresholds). For both pre- and post-treatment fMRI data, estimates for the strength of