The role of long-term physical exercise on performance and brain activation during the Stroop colour word task in fibromyalgia patients

S. Martinsen1,2, P. Flodin3,4, J. Berrebi1,2, M. Löfgren5, I. Bileviciute-Ljungar5, K. Mannerkorpi6, M. Ingvar1,2, P. Fransson7,8 and E. Kosek1,2

1Department of Clinical Neuroscience, Osher Center for Integrative Medicine, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden, 2Department of Neuroradiology, Karolinska University Hospital, Stockholm, Sweden, 3Center for Demographic and Aging research, Umeå University, Umeå, Sweden, 4Umeå Center for Functional Brain Imaging, Umeå University, Umeå, Sweden, 5Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden, 6Department of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden, and 7Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Summary

The Stroop colour word test (SCWT) has been widely used to assess changes in cognitive performance such as processing speed, selective attention and the degree of automaticity. Moreover, the SCWT has proven to be a valuable tool to assess neuronal plasticity that is coupled to improvement in performance in clinical populations. In a previous study, we showed impaired cognitive processing during SCWT along with reduced task-related activations in patients with fibromyalgia. In this study, we used SCWT and functional magnetic resonance imaging (FMRI) to investigate the effects of a 15-week physical exercise intervention on cognitive performance, task-related cortical activation and distraction-induced analgesia (DIA) in patients with fibromyalgia and healthy controls. The exercise intervention yielded reduced fibromyalgia symptoms, improved cognitive processing and increased task-related activation of amygdala, but no effect on DIA. Our results suggest beneficial effects of physical exercise on cognitive functioning in FM.

Introduction

Fibromyalgia (FM) entails hypersensitivity to painful stimuli (Kosek et al., 1996a,b) and exhibited dysfunction of several pain regulatory mechanisms, such as condition pain modulation (CPM) (Kosek & Hansson, 1997; Lautenbacher & Rollman, 1997) and exercise-induced hypoalgesia (Kosek et al., 1996a, b; Lannersten & Kosek, 2010). Further support for a dysfunction of central pain inhibitory mechanisms in FM has been provided by functional magnetic resonance imaging (fMRI) studies that have assessed brain activation during evoked pain. Patients with FM had reduced activation of rostral anterior cingulate cortex (rACC) (Jensen et al., 2009) and weaker connectivity between rACC and amygdala, hippocampus and brainstem, respectively, (Jensen et al., 2012) compared to healthy controls (HC). There are several areas in the brain that have overlapping role for both pain and cognition, which has led to a theory suggesting that the cognitive complaints in chronic pain patients are due to the fact that processing pain takes over resources needed for cognition, the so-called limited resource theory (Moriarty et al., 2011). The latter is supported by reports of poorer cognitive test performance in chronic pain patients compared to controls (Rathbone et al., 2016). Self-reported cognitive complaints, as well as poorer performance during cognitive testing compared to controls, have also been reported in patients with fibromyalgia (Rathbone et al., 2016), although with inconsistent results and not always remaining after correction for depression and anxiety (Suhr, 2003; Genlonch et al., 2016). However, impairments of executive functions, particularly selective attention, processing speed and inference inhibition as assessed by the Stroop colour word task (SCWT), have been documented in patients with fibromyalgia and remained even when adjusted for mood (Cherry et al., 2014; Genlonch et al., 2016). Despite the fact that no definite conclusions can be drawn regarding perturbations in cognition in patients with FM, there is reason to assume that similar brain areas that show aberrations in activation during pain processing are also involved in cognition.

In line with the shared neural circuits of pain and cognition, physical exercise has been shown to have beneficial effects by reducing pain sensitivity (Kolyn, 2002; Kolyn & Umeda, 2006) and improving cognitive function (Hillman et al., 2008; Loprinzi et al., 2013) in healthy subjects. Various forms of physical exercise are also highly recommended for the treatment of
FM symptoms and have been shown to reduce pain and tenderness as well as to improve function and well-being in patients with FM (Mannerkorpi, 2005; Busch et al., 2013; Larsson et al., 2015). Patients with FM tend to be deconditioned (Kulshreshtha & Deepak, 2013) and to engage in less strenuous activities than HCs (Kop et al., 2005). Therefore, increasing levels of physical activity levels in patients with FM could potentially have a substantial impact on their cognitive ability, such as executive functions assessed by SCWT.

In a previous fMRI study, we investigated the interactions between chronic pain and cognition by assessing the attention-related cerebral responses during the SCWT (colour-based congruency/incongruency of words) and the effects of SCWT on pain sensitivity in patients with FM and a HC cohort (Martinsen et al., 2014). Compared to HCs, patients exhibited longer reaction times (RTs) during both congruent and incongruent word stimuli, but the group difference was more pronounced for the incongruent stimuli. Thus, we found evidence of slower task-related differences in cognitive processing in patients with FM that were accompanied with reduced activation in the caudate nucleus and hippocampus in patients with FM. Furthermore, we showed that patients with FM did not differ from HCs regarding DIA.

The present studied cohort represents a subgroup of the previously study of patients with FM and HCs (Martinsen et al., 2014). Here, we assessed the effect on behaviour and cerebral activation from the SCWT after a resistance exercise intervention that lasted 15 weeks. We hypothesized that RTs would improve in both cohorts following exercise and particularly pronounced for the incongruent stimuli in patients with FM. Additionally, we hypothesized that these improvements would be related to increased activation of the caudate nucleus and hippocampus in patients with FM. Notably, previous studies in healthy individuals have revealed a positive correlation between SCWT performance and activity in the dorso-lateral prefrontal cortex (diPFC, Floden et al., 2011). Furthermore, acute exercise has been shown to have a positive effect on SCWT performance, a finding that was linked to increased activity in the diPFC (Yanagisawa et al., 2010). Thus, we hypothesized that the improved SCWT performance in the HC cohort would be related to increased activation of the diPFC. Finally, given that levels of DIA were normal in patients with FM at baseline, we did not expect any changes after intervention.

**Methods**

**Subjects**

Subjects were recruited by newspaper advertisement to participate in a multicentre experimental study (ClinicalTrials.gov identification number: NCT01226784) where patients with FM were randomized to physical exercise or relaxation therapy. The results from this trial have been published earlier (Larsson et al., 2015). This study was performed in the Stockholm cohort only and relies on data from participants who participated in the intervention.

FM patients

Thirty-one women diagnosed with FM were initially included in the study. Two patients were excluded (one due to not meeting MRI safety criteria and one due to inability to participate) at baseline. Ten participants dropped out of the intervention, leaving data from nineteen FM to be analysed (mean age 49.6 years, range 25–64 years). The average duration of FM was 8 years (range 1–16 years). Functional magnetic resonance imaging (fMRI) data from one participant were not collected due to technical problems.

Inclusion criteria for women with FM were to be of working age, 20–65 years, and meeting the ACR-1990 classification criteria for FM (Wolfe et al., 1990). Exclusion criteria were high blood pressure (>160/90 mmHg), osteoarthritis in hip or knee, other severe somatic or psychiatric disorders, other primary causes of pain than FM, high consumption of alcohol (Audit > 6), participation in a rehabilitation programme within the past year, regular 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, NSAIDs or hypnotics for 48 h prior to examinations. All patients declared that they had refrained from hypnotics, NSAIDs, acetaminophen and tramadol/other analgesics at least 48 h prior to study participation [48 h before study one and 72 h before study two (fMRI)]. All patients had a physical examination by a specialist in rehabilitation medicine to ensure that they fulfilled the inclusion criteria.

Twenty-three healthy control female subjects were recruited to the exercise intervention. One control had to be excluded due to MR scan showing signs of neuroinflammatory changes and a further two controls dropped out from the intervention, resulting in that the final cohort consisted of 20 women (mean age 47.2 years, range 20–63 years). Due to technical failure, fMRI was not collected in two participants.

The regional ethics committee in Stockholm approved the study, and written informed consent was obtained from all participants.

**Material**

**Procedure**

Before and following the exercise intervention, all subjects were familiarized with the SCWT and the pressure algometer and assessed regarding pressure pain modulation during SCWT. Participants returned on the following day for the SCWT fMRI scan.

**Questionnaires**

All participants completed questionnaires regarding health-related quality of life (Short Form-36 (SF-36)) (Contopoulos-Ioannidis et al., 2009), hospital anxiety and depression scale, (HADS) (Bjelland et al., 2002) and pain intensity ratings
(100-mm visual analogue scale, VAS) before and following the exercise intervention. The VAS was anchored by the phrases ‘no pain’ and ‘worst imaginable pain’, respectively. Changes in FM symptoms (fibromyalgia impact questionnaire, FIQ, Bennett, 2005) were analysed.

Pressure algometry, pressure pain modulation and SWCT measurements outside the MR scanner

Pressure pain thresholds (PPTs) were assessed using a pressure algometer (Somedic Sales AB). The pressure algometer had a gun-shaped handle with a 1 cm², circular, flat rubber tip on the end. The chosen rate was approximately 50 kPa s⁻¹. Further details regarding the algometer are given Martinsen et al. (2014). The algometer was calibrated for accuracy before each examination.

Images were presented on a 17” LCD screen with a resolution of 1024 × 768 pixels. Participants were given a response button box with four response buttons coloured in red, green, yellow and blue. For the SCWT, the colours red, green and yellow together with the Swedish translation of these words made up the visual presentation. Stimuli were of two kinds presented in two separate sessions (10 min each). Congruent visual stimuli (e.g. ‘yellow’ displayed in the colour yellow) and incongruent visual stimuli (e.g. ‘green’ displayed in red colour) were shown. The exact timing of the stimuli, the instructions given to the participants as well as information on how measurement of PPTs during the SCWT was carried out have previously been described in Martinsen et al. (2014).

Functional magnetic resonance imaging (fMRI)

Functional magnetic resonance imaging (fMRI) data were collected using a 3.0 Tesla MR scanner (Discovery MR750, GE, 32-channel head-coil). The SCWT task was performed by all participants during two separate fMRI sessions. For each session, 84 BOLD fMRI image volumes were acquired (EPI, TR/TE = 2500/30 ms, flip = 90°, Field of View = 288 × 288 mm, matrix size = 128 × 128, slice thickness = 3 mm, interleaved slice acquisition) resulting in a voxel size of 3 × 3 × 3 mm³. Each SWCT fMRI session contained an equal distribution of congruent and incongruent trials, and the order of trials was randomized within each fMRI session. The interstimuli interval was jittered between 6 and 10 s (mean 8 s). A fixation-cross preceded each stimulus for 500 ms followed by a blank screen for 1500 ms. The colour word stimuli were displayed for 3000 ms. T1- and T2-weighted images were obtained for screening and anatomical reference purposes.

Exercise intervention

A fifteen-week exercise programme with two sessions each week was carried out under supervision from a physiotherapist (PT) (Larsson et al., 2015). Before the participants started the intervention, they had an individual meeting with a PT who tested their one repetition maximum (1RM) and tolerance before deciding on the initial load of each exercise. Each participant received individual instructions for every exercise. Each session lasted for about 1 h. A detailed account of contents of the exercise schedule is provided in Larsson et al. (2015).

Statistics

SPSS 21 (IBM SPSS Software, NY, USA) was used for statistical analysis of all data except fMRI. Questionnaires were analysed using a repeated measures ANOVA with the within-subject factor INTERVENTION (pre- and postexercise) and the between-subject factor GROUP (FM patients and controls). Analysis of within-group changes in the FM group regarding FIQ was made using Student’s paired t-test. Group differences in absolute PPTs before SCWT were assessed by repeated measures ANOVA with the factors GROUP (FM and HC), EXERCISE (post and pre) and ASSESSMENT (4 PPTs assessments before SCWT, 2 at left m. quadriceps and 2 at right m. quadriceps, respectively). All repeated measure ANOVA tests employed the Greenhouse-Geisser correction to correct for violation of sphericity in repeated measures designs.

Analysis of pressure pain modulation during SCWT

To assess the effect of SCWT on pressure pain sensitivity, the relative change in PPTs at m. quadriceps during SCWT was analysed. The PPTs were normalized (i.e. each PPT value was divided by the individual’s first PPT measure) (Lannersten & Kosek, 2010). The effect of SCWT and exercise intervention on PPTs was analysed using a repeated measures ANOVA with the within-subject factors CONGRUENCY (two levels), TIME (seven levels, once before, five times during and once 10 min following SCWT) and EXERCISE (two levels) and the between-subject factor GROUP.

Analysis of reaction times during SCWT

Putative differences in RTs at baseline were assessed by a repeated measures ANOVA with the within-subject factor CONGRUENCY and the between-subject factor GROUP. The effect of congruency and exercise intervention on RTs was analysed using a repeated measures ANOVA with the within-subject factors CONGRUENCY and EXERCISE and the between-subject factor GROUP. In order to assess an exercise-dependent improvement specific to the Stroop effect, the RTs for congruent trials were subtracted from the RTs for incongruent trials for each participant both prior to and following intervention. For all ANOVA, post hoc analysis were performed using Student’s independent samples t-test for between-group analysis and Student’s paired t-test for within-group analysis.
Analysis of functional magnetic resonance imaging (fMRI) data

Functional magnetic resonance imaging (fMRI) data were analysed using SPM8 (Friston et al., 1995). EPI images were realigned and normalized to the canonical EPI template in the standard Montreal Neurological Institute (MNI) space. Finally, the images were smoothed using a 8 mm full-width-at-half-maximum Gaussian kernel. For each individual subject, first-level analysis was performed using a general linear model that concatenated imaging data from both sessions. Stimulus onset times of congruent and incongruent stimuli were entered as regressors of interest, and movement parameters were entered as covariates of no interest. Brain activity at a group level was assessed using a random, second-level analysis of the statistical parametric images obtained at the first level. To evaluate between-group differences in brain activity, two-sample t-tests were used. Within-group differences were assessed using paired t-tests. Clusters of activity smaller than 20 contiguous voxels were not reported. Given the limited sample size and the rather explorative character of the study, whole-brain voxel-level analysis was not performed. Given the limited sample size and the rather explorative character of the study, whole-brain voxel-level analysis was not performed. Given the limited sample size and the rather explorative character of the study, whole-brain voxel-level analysis was not performed. Given the limited sample size and the rather explorative character of the study, whole-brain voxel-level analysis was not performed. Given the limited sample size and the rather explorative character of the study, whole-brain voxel-level analysis was not performed. Given the limited sample size and the rather explorative character of the study, whole-brain voxel-level analysis was not performed.

Results

Questionnaires

Descriptive data from the questionnaires are presented in Table 1. The FIQ ratings decreased following exercise in patients with FM (P = 0.048), suggesting an improvement of FM symptoms. Furthermore, for the SF-36 PCS ratings we found a statistically significant effect of GROUP (F = 35.9, P<0.0001) and INTERVENTION (F = 4.2, P = 0.048), but no significant interaction between the factors, thus showing that exercise improved ratings of SF-36 PCS in both groups. For the remaining factors (VAS pain, SF-36 MCS, HAD-D and HAD-A), there was a statistically significant effect of GROUP only (P<0.0001).

Distraction-induced analgesia

The average absolute PPT at m. quadriceps before SWTC was significantly lower for patients with FM (pre-intervention: mean = 186.4 kPa, SD = 93.0; postintervention: mean = 190 kPa, SD = 91.93) than for healthy controls (pre-intervention: mean = 312.6 kPa, SD = 107.3, postintervention: mean = 284.88 kPa, SD = 100.15) (P<0.001). In addition, patients with FM showed lower absolute PPTs at all times during and after incongruent and congruent SCWT pre- and postintervention (P<0.05). Regarding the effects of exercise on the SCWT-related changes in normalized PPTs we found a significant effect of TIME (df= 3,7, F = 27.7, P<0.0001), but no significant effects regarding CONGRUENCE, EXERCISE or GROUP and no statistically significant interactions between the factors. Normalized PPTs were higher during SCWT (congruent and incongruent) in both groups at all times compared to before SCWT, pre- as well as postintervention (P<0.001; Fig. 1).

Reaction times for the Stroop Word Colour Task

The 2 × 2 × 2 ANOVA revealed a significant main effect of CONGRUENCY (F = 102.91, P<0.0001) and GROUP (F = 1654.83, P<0.034). The main effect of EXERCISE was not statistically significant. The only interaction that was statistically significant was between CONGRUENCY and EXERCISE (F = 7.12, P = 0.012). Post hoc analysis revealed that HC improved their RT significantly for both the congruent (P = 0.031) and incongruent (P = 0.027) stimuli (Fig. 2). However, this was not observed in the FM group. The difference in RTs between incongruent and congruent stimuli postintervention was significantly smaller for patients with FM (P = 0.028), but not in HC compared to baseline (Fig. 3). The differences in RTs between incongruent and congruent images were larger in patients with FM compared to HC pre- (P<0.05), but not postintervention.

Table 1 Effects of exercise on pain, FM symptoms, health-related quality of life and psychological symptoms.

|                      | FM before | FM after | HC before | HC after | Group diff | Change |
|----------------------|-----------|----------|-----------|----------|------------|--------|
| VAS pain             | 44.6 ± 17.5 | 41.1 ± 21.0 | 0.8 ± 2.4 | 0.3 ± 1.1 | P<0.001 NS |        |
| FIQ total            | 59.9 ± 16.0 | 54.7 ± 19.8 | NA        | NA       | P<0.05*    |        |
| SF36-PCS             | 33.2 ± 11.7 | 36.6 ± 16.4 | 54.7 ± 3.1 | 55.7 ± 2.8 | P<0.001    |        |
| SF36-MCS             | 35.3 ± 10.0 | 38.2 ± 11.8 | 50.9 ± 5.9 | 50.3 ± 7.2 | P<0.001 NS |        |
| HAD-D                | 11.3 ± 11.1 | 7.53 ± 3.7  | 2.1 ± 2.1 | 2.6 ± 2.7 | P<0.001 NS |        |
| HAD-A                | 8.63 ± 4.4  | 7.79 ± 4.8  | 2.7 ± 2.6 | 2.9 ± 2.9 | P<0.001 NS |        |

Pain VAS, pain intensity rated on 100-mm visual analogue scale; FIQ, fibromyalgia impact questionnaire; SF36-PCS, short form-36 physical compact score; SF36-MCS, short form-36 mental compact score (original 0–100 scoring algorithms based on the summed ratings method); HADS-D, Hospital anxiety and depression scale, depression ratings; HADS-A, Hospital anxiety and depression scale, anxiety ratings; NA, not applicable.

Mean scores and standard deviations are presented.

*FM group only.
Functional magnetic resonance imaging results: between-group effects before intervention

As this study included data from a subcohort of a larger sample that previously have been studied at baseline (Martin-sen et al., 2014), we wanted to ensure that our previous baseline results still hold in the subcohort. Contrasting HC > FM during incongruent versus congruent stimuli at pre-intervention, we could corroborate our previous findings; that is, HC had a stronger activation in the caudate nucleus and temporal lobes but not in the hippocampus (Table 2). No regions in patients with FM showed stronger activity than HC at pre-intervention. Postintervention, we found no regions that were more active in HC compared to patients with FM when contrasting incongruent-congruent stimuli; however, patients with FM had a stronger activity in the cerebellum and putamen (Table 3).

Discussion

Our main finding was a differential effect of the exercise intervention on the speed of cognitive processing during SCWT in patients with FM and healthy controls. The difference in RTs between the cognitively more demanding incongruent task was reduced in patients with FM following the intervention. Given our previous findings of a larger discrepancy between congruent and incongruent RTs in patients with FM compared to HC (Martin-sen et al., 2014), the current results indicate a normalization of executive function related to task difficulty, that is reduced inference inhibition, in patients with FM following a long-term intervention. In contrast, this was not accompanied by a normalized task-related activation of the caudate nucleus and hippocampus. Rather, our results suggest an increased bilateral amygdala activation in the FM cohort. The HC cohort showed a decrease in RTs...
during incongruent as well as congruent stimuli alike. Thus, we found no evidence that the intervention improved executive function related to task difficulty for HC. Furthermore, intervention did not have an effect on DIA or PPTs in either group. Given the normal function of DIA pre-intervention in HC, we did not anticipate any major group differences post-intervention. However, an improved DIA is plausible as physical activity is associated with more efficient DIA in physically active than sedentary patients with FM (Ellingson et al., 2012). Finally, we found a beneficial effect of intervention on the overall severity of FM symptoms (reduced FIQ ratings) and slightly improved health-related quality of life on the physical domains (SF-36 PCS) in both groups.

In accordance with our prior hypothesis, we found an improvement of executive function related to task difficulty in patients with FM indicating reduced inference inhibition. However, the patients still had longer RTs during incongruent as well as congruent stimuli compared to controls suggesting reduced processing speed in FM. Based on previous findings (Martinsen et al., 2014), we hypothesized that improved executive function following intervention would be accompanied by a normalization of brain activity in the caudate nucleus and hippocampus. Although we detected significantly reduced activation of the caudate nucleus in patients with FM prior, but not after intervention, a direct comparison of post- versus pre-intervention activity maps did not show any significant differences. Hence, our prior hypothesis regarding normalization of brain activity in the hippocampus and caudate nucleus in relation to the cognitive processing of the Stroop task could not be confirmed.

A whole-brain analysis revealed increased activation of the bilateral amygdala and the right temporal lobe when contrasting post- versus pre-intervention for the incongruent versus congruent SCWT contrast in patients with FM. Interestingly, previous studies have reported structural abnormalities of the amygdala in patients with FM (Lutz et al., 2008), as well as decreased pain-related connectivity between the amygdala and the rACC (Jensen et al., 2012). The amygdala is known to be involved in arousal (Zald, 2003), emotionally salient stimuli (Zhong et al., 2011) and playing a pivotal role in the relation between pain and stress systems (Clewett et al., 2013). Hence, it seems plausible that the increase in amygdala activation in patients with FM might be related to the observed increase in performance of patients with FM to the incongruent, more demanding stimuli. Moreover, amygdala is one of the brain areas that involved in regulating the hypothalamo–pituitary–adrenal (HPA) axis (Flandreau et al., 2012) as well as the sympathetic nervous system (Beissner et al., 2013), both implicated in the response to pain, stress and physical exercise. To this end, Patients with FM have been shown to exhibit hypoactivity of the HPA axis (Croford et al., 1994) as well as hyporeactivity of the HPA axis during static muscular work (Kadetoff & Kosek, 2010). Moreover, female patients...
with FM have an abnormal diurnal cortisol secretion pattern, with lower overall levels of cortisol (Crofford et al., 1994; Tak et al., 2011), a finding that was related to the duration of FM, which has been interpreted as an exhaustion of the system over time (Riva et al., 2010). In the CNS, cortisol is implicated in the inhibition of amygdala by the medial prefrontal cortex (Moriarty et al., 2011) and if this mechanism is indeed dysfunctional in FM, a hyperactivation of the amygdala is to be expected. Physical activity has been found to have a positive effect on coping with mental stressors in healthy participants and is correlated to less activity of the HPA axis as measured by cortisol levels (Puterman et al., 2011). Hypothetically, the beneficial effects of exercise on FM symptoms could be accompanied by a partial normalization of the HPA axis function, thus increasing the tonic inhibition of the amygdala by the prefrontal cortex (Moriarty et al., 2011) and rendering the amygdala more responsive during the demanding stimuli.

Furthermore, studies using heart rate variability (HRV) have shown that patients with FM have an autonomic imbalance characterized by reduced HRV, relative basal sympathetic hyperactivity and parasympathetic hypoactivity, combined with sympathetic hyporeactivity during stress or physical exercise (Meeus et al., 2013). Longitudinal studies measuring HRV have shown that long-term physical exercise increases HRV and changes autonomic balance in healthy women in favour of parasympathetic activity (Earnest et al., 2008). The finding has been observed in patients with FM following 16 weeks of resistance exercise training (Figueroa et al., 2008), thus normalizing the basal sympathetic hyperactivity in FM. However, recent study failed to reproduce this finding in both FM patients and HC; hence, the literature is not conclusive on this issue (Gavi et al., 2014). But the left amygdala has been implicated in the regulation of autonomic activity, particularly the sympathetic tone (Thayer et al., 2012; Beissner et al., 2013). Therefore, normalization of the autonomic activity following exercise would hypothetically be accompanied by a reduction (normalization) of basal activity in amygdala and the increases in HRV following exercise would be in accordance with our finding of an increased amygdala reactivity.

Given the minimal improvement in pain intensity corresponding to a reduction of 3-5 mm on a 100 mm VAS (NS) and the statistically non-significant improvements in mood (HAD-D: 11·3–7·5, and HAD-A: 8·6–7·8), we do not think it likely that reductions in pain or mood disturbances explained the improved SCWT performance in our patients. Furthermore, although depression and anxiety has been shown to influence cognitive function in FM, previous studies have shown that this is less pronounced regarding SCWT performance (Cherry et al., 2014; Genlonch et al., 2016).

The HCs showed an improvement in RT reflecting a general positive effect on processing speed. Good SCWT performers often show an increased activation of the dLPFC, a finding that has also been observed directly after exercise (Yanagisawa et al., 2010). However, although this effect was not replicated in the FM cohort, it should be borne in mind that a lack of a behavioural interaction, that is, specific improvement of RT on the incongruent stimuli and therefore an absence of activity in dLPFC might be due to the task not being sufficiently challenging.

We did not include participants who did not partake in the intervention. Therefore, although we analysed the differential effects of the intervention on patients with FM and HC, we had no inactive control group. Finally, we choose to include patients on antidepressants/anticonvulsants to avoid selection bias. However, our baseline analysis indicated that this choice did not influence the fMRI results (Martinsen et al., 2014).

**Conclusion**

In conclusion, the intervention had different effects on the speed of cognitive processing during SCWT in patients with FM and healthy controls. We found evidence of normalization of cognitive processing related to task difficulty in patients with FM reflected as an increased amygdala activation. In
contrast, HC showed decreased RTs during incongruent as well as congruent stimuli alike. Exercise did not have an effect on distraction-induced analgesia or pressure pain thresholds in either group, but diminished the overall severity of FM symptoms.

Acknowledgments

This study was supported by grants from the Swedish Rheumatism Association, the Stockholm County Council, the Swedish Foundation for Strategic Research, the Swedish Research Council K2013-52X-22199-01-3 and Karolinska Institutet Foundation.

Conflicts of interest

None of the authors report any conflict of interests. The manuscript meets the guidelines for ethical conduct and report of research.

References

Beissner F, Meissner K, Bar KJ, et al. The autonomic brain: an activation likelihood estimation meta-analysis for central processing of autonomic function. J Neurosci (2013); 33: 10503–10511.

Bennett R. The Fibromyalgia Impact Questionnaire (FIQ): a review of its development, current version, operating characteristics and uses. Clin Exp Rheumatol (2005); 23: S154–S162.

Bjelland I, Dahl AA, Haug TT, et al. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res (2002); 52: 69–77.

Busch AJ, Webber SC, Richards RS, et al. Resistance exercise training for fibromyalgia. Cochrane Database Syst Rev (2011); 12: CD010884.

Cherry BJ, Zettel-Watson L, Shimizu R, et al. Cognitive performance in women aged 50 years older with and without fibromyalgia. J Genontology B Psychol Sci Sci (2014); 69: 199–208.

Clewett D, Schoeck A, Mathes M. Amygdala functional connectivity is reduced after the cold pressor task. Brain Res (2013); 1539: 95–104.

© 2017 The Authors. Clinical Physiology and Functional Imaging published by John Wiley & Sons Ltd on behalf of Scandinavian Society of Clinical Physiology and Nuclear Medicine. 38, 3, 508–516
Lutz J, Jager L, de Quervain D, et al. White and gray matter abnormalities in the brain of patients with fibromyalgia: a diffusion-tensor and volumetric imaging study. *Arthritis Rheum* (2008); 58: 3960–3969.

Mannerkorpi K. Exercise in fibromyalgia. *Curr Opin Rheumatol* (2005); 17: 190–194.

Martinsen S, Flodin P, Berrebi J, et al. Fibromyalgia patients had normal distraction related pain inhibition but cognitive impairment reflected in caudate nucleus and hippocampus during the Stroop Color Word Test. *PloS One* (2014); 9: e108637.

Meeus M, Goubert D, De Backer F, et al. Heart rate variability in patients with fibromyalgia and patients with chronic fatigue syndrome: a systematic review. *Semin Arthritis Rheum* (2013); 43: 279–287.

Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: a review of clinical and preclinical research. *Prog Neurobiol* (2011); 93: 385–404.

Puterman E, O’Donovan A, Adler NE, et al. Physical activity moderates effects of stressor-induced rumination on cortisol reactivity. *Psychosom Med* (2011); 73: 604–611.

Rathbone M, Parkison W, Rehman Y, et al. Magnitude and variability of effect sizes for the association between chronic pain and cognitive test performances: a meta-analysis. *Br J Pain* (2016); 10: 141–155.

Riva R, Mork PJ, Westgaard RH, et al. Fibromyalgia syndrome is associated with hypocortisolism. *Int J Behav Med* (2010); 17: 223–233.

Suhr JA. Neuropsychological impairment in fibromyalgia. Relation to depression, fatigue, and pain. *J Psychosom Res* (2003); 55: 321–329.

Tak JM, Cleare AJ, Ormel J, et al. Meta-analysis and meta-regression of hypothalamic-pituitary-adrenal axis activity in functional somatic disorders. *Biol Psychol* (2011); 87: 183–194.

Thayer JF, Ahs F, Fredrikson M, et al. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. *Neurosci Biobehav Rev* (2012); 36: 747–756.

Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* (1990); 33: 160–172.

Yanagisawa H, Dan I, Tsuzuki D, et al. Acute moderate exercise elicits increased dorsolateral prefrontal activation and improves cognitive performance with Stroop test. *NeuroImage* (2010); 50: 1702–1710.

Zald DH. The human amygdala and the emotional evaluation of sensory stimuli. *Brain Res Brain Res Rev* (2003); 41: 88–123.

Zhong M, Wang X, Xiao J, et al. Amygdala hyperactivation and prefrontal hypoactivation in subjects with cognitive vulnerability to depression. *Biol Psychol* (2011); 88: 233–242.