Three weeks of exercise therapy altered brain functional connectivity in fibromyalgia inpatients

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ABSTRACT

Background: Fibromyalgia (FM) is a chronic pain syndrome characterized by widespread pain, tenderness, and fatigue. Patients with FM have no effective medication so far, and their activity of daily living and quality of life are remarkably impaired. Therefore, new therapeutic approaches are awaited. Recently, exercise therapy has been gathering much attention as a promising treatment for FM. However, the underlying mechanisms are not fully understood, particularly, in the central nervous system, including the brain. Therefore, we investigated functional connectivity changes and their relationship with clinical improvement in patients with FM after exercise therapy to investigate the underlying mechanisms in the brain using resting-state fMRI (rs-fMRI) and functional connectivity (FC) analysis.

Methods: Seventeen patients with FM participated in this study. They underwent a 3-week exercise therapy on inpatient basis and a 5-min rs-fMRI scan before and after the exercise therapy. We compared the FC strength of sensorimotor regions and the mesocortico-limbic system between two scans. We also performed a multiple regression analysis to examine the relationship between pre-post differences in FC strength and improvement of patients' clinical symptoms or motor abilities.

Results: Patients with FM showed significant improvement in clinical symptoms and motor abilities. They also showed a significant pre-post difference in FC of the anterior cingulate cortex and a significant correlation between pre-post FC changes and improvement of clinical symptoms and motor abilities. Although sensorimotor regions tended to be related to the improvement of general disease severity and depression, brain regions belonging to the mesocortico-limbic system tended to be related to the improvement of motor abilities.

Conclusion: Our 3-week exercise therapy could ameliorate clinical symptoms and motor abilities of patients with FM, and lead to FC changes in sensorimotor regions and brain regions belonging to the mesocortico-limbic

system. Furthermore, these changes were related to improvement of clinical symptoms and motor abilities. Our findings suggest that, as predicted by previous animal studies, spontaneous brain activities modified by exercise therapy, including the mesocortico-limbic system, improve clinical symptoms in patients with FM.

1. Introduction

Fibromyalgia (FM) is a chronic pain syndrome. The primary symptoms of this syndrome are muscle, joint, and bone pain (Wolfe et al., 2010). It is also accompanied by tenderness, fatigue, and other symptoms (Weir et al., 2006). It mainly affects women between 40 and 60 years of age (Wolfe et al., 1995). Its prevalence rate is approximately 2% (Wolfe et al., 1995). The activity of daily living (ADL) and quality of life (QOL) are remarkably impaired in patients with FM. However, many cases are refractory to multiple therapeutic approaches (Carville et al., 2008). Therefore, new therapeutic approaches are awaited.

Recently, exercise therapy has been attracting much attention as a promising treatment for FM (Busch et al., 2011; Masquelier & D'haeyere, 2021). This therapy is thought to be based on exercise-induced hypoalgesia (EIH). EIH is a phenomenon that pain sensitivity temporarily decreases after a single bout of physical exercise (Rice et al., 2019). The phenomenology and physiology of EIH have been extensively studied in animals as well as in pain-free and chronic pain populations (Rice et al., 2019). Although EIH has been observed in patients with various chronic pain conditions, including FM (Meeus et al., 2010; Staud et al., 2010; Kosek et al., 2013; Christensen et al., 2017), the physiological mechanisms of EIH remain incompletely understood. So far, it is thought that the interaction between the opioid and endocannabinoid systems has a critical role in EIH (Koltyn et al., 2014). The interaction between the opioid and serotonergic systems also seems to be essential for EIH (Lima et al., 2017). Furthermore, some studies suggest that the immune system (Light et al., 2009) and autonomic nervous system (Malfliet et al., 2018) are involved in EIH.

Meanwhile, the effectiveness of exercise therapy on chronic pain has achieved a consensus. A meta-analysis of 24 randomized controlled trials for patients with chronic low back pain (Malfliet et al., 2019), neck pain (Sterling et al., 2019), and osteoarthritis (Rice et al., 2019) revealed that exercise therapy improves their pain and dysfunction. Moreover, for patients with FM, four Cochrane systematic reviews have suggested that exercise therapy can effectively improve QOL, pain, tiredness, bodily function, and muscle stiffness (Bidonde et al., 2014, 2017, 2019; Kim et al., 2019). In addition, in the EULAR revised recommendations for managing fibromyalgia, exercise therapy, particularly aerobic exercise and strength training, are recommended (Macfarlane et al., 2017). However, as with the physiological mechanisms of EIH, the underlying mechanisms of exercise therapy for chronic pain are not fully understood. Several studies pointed out the importance of cognitive approaches, such as education and cognitive behavioral therapy (Elbers et al., 2018; Wood et al., 2019; Marris et al., 2021), and behavioral medicine approaches (Malfliet et al., 2019; Sterling et al., 2019; Rice et al., 2019) in combination with exercise therapy. These findings suggest that some other factors besides EIH may contribute to the effectiveness of exercise therapy in the treatment of chronic pain. Therefore, investigating the underlying mechanisms of exercise therapy itself, as well as that of EIH, is necessary.

In recent years, the combination of resting-state functional MRI (rs-fMRI) and functional connectivity (FC) analysis has frequently been used as a tool for investigating functional brain alterations in patients with a wide variety of diseases (Lee et al., 2013; Filippi et al., 2019). This approach focuses on spontaneous brain activity and functional coupling between distant brain regions. Using this approach, many groups reported functional alterations in patients with chronic pain and the relationship between symptoms of chronic pain, such as pain intensity and anxiety, and FC strength (Thorp et al., 2018; Pfannmöller and Lotze, 2019). In particular, several previous studies reported that FC between the medial prefrontal cortex (mPFC) or the posterior cingulate cortex (PCC) and insula is closely related to the development and maintenance of FM (Napadow et al., 2010; Ichesco et al., 2014; Čeko et al., 2020). On the other hand, only one study examined the underlying mechanisms of exercise therapy for patients with FM using this approach, by comparing pre-post differences in functional connectivity and clinical symptoms in the same group of FM patients (Flodin et al., 2015). Therefore, we attempted to elucidate the underlying mechanisms of exercise therapy in patients with FM from the brain function perspective by using rs-fMRI and FC analysis.

2. Methods

2.1. Participants

Seventeen patients with FM participated in this study (58.2 ± 13.7 years old). All of them were females. They were diagnosed by pain specialists based on the American College of Rheumatology 1990 criteria for fibromyalgia (Wolfe et al., 1990). All participants gave informed written consent before study enrollment. This study was approved by the Institutional Review Board of Osaka University Hospital (approval numbers: 13212-9 and 19245) and was conducted by the Declaration of Helsinki and related guidelines.

2.2. Exercise therapy and assessment

The patients underwent a 3-week exercise therapy on inpatient basis. This exercise therapy consisted of aerobic exercise, range of motion, and strength training. Exercise intensities for each patient were adjusted to an 11–15 Borg scale for strength training and a 60% heart rate max calculated by Karvonen formula for aerobic exercise and strength training. Physical therapists instructed and supervised each patient throughout the 3-week therapy.

To confirm the effect of the exercise therapy on patients' condition, we assessed the clinical condition of each patient before and after the therapy by using the following clinical measures: the Japanese version of the Fibromyalgia Impact Questionnaire (JFIQ) (Burckhardt et al., 1991; Bennett, 2005; Osada et al., 2011), pain intensity, Pain Disability Assessment Scale (PDAS) (Yamashiro et al., 2011), Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983; Kitamura, 1993; Matsudaira et al., 2009), Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995; Matsuoka & Sakano, 2007), EuroQol 5 dimensions 3-level (EQ-5D-3L) (EuroQol Group, 1990; Tsuchiya et al., 2002), Pain Self-Efficacy Questionnaire (PSEQ) (Nicholas, 2007; Adachi et al., 2014), and Athens Insomnia Scale (AIS) (Soldatos et al., 2000; Okajima et al., 2013). Moreover, to confirm motor ability improvement by the therapy, we assessed the following motor ability indices (Table 1): walking speed, cadence, stride, daily step counts, one-leg standing time, ergometer cycling intensity, and ergometer cycling time.

2.3. fMRI data acquisition and analysis

MRI imaging was performed at Osaka University Hospital using a 3-Tesla scanner (General Electric Discovery750, Waukesha, Wisconsin, United States). Anatomical images were acquired with a high-resolution 3D T1-weighted image sequence ($1 \times 1 \times 1$ mm^3 voxel size). One hundred fifty volumes of functional images were obtained using a single-shot gradient-echo echo-planar imaging sequence. Scanning parameters were as follows: repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, the number of slices = 40, matrix size = 64 × 64, field of

Table 1

Motor ability indices.

Index name	Definition	Evaluation content
walking speed	walking distance per unit of time	walking ability
cadence	frequency of steps	walking ability
stride	distance between consecutive steps	walking ability
daily step counts	the number of steps a day	general endurance and activity
one-leg standing time	the duration that one can stand on one leg	lower-limb muscle strength and balance ability
ergometer cycling intensity	maximum workload at target motor intensity	lower-limb muscle strength and general endurance
ergometer cycling time	the duration that one can continue to cycling at target motor intensity	lower-limb muscle strength and general endurance

Note: "target motor intensity" was set at 60% of heart rate maximum calculated according to the Karvonen formula.

view = 220×220 mm, slice thickness = 3.5 mm without gap. The slice acquisition order was interleaved (bottom-to-up). Participants were instructed to be awake and keep their eyes closed during the 5-minute rs-fMRI scan. Participants' arousal was orally confirmed just before and after an rs-fMRI scan by MRI operators, and whether each participant had been able to be awake during an rs-fMRI scan was additionally confirmed after the entire MRI scanning session.

Rs-fMRI data were processed with SPM12 (version 6906, https ://www.fil.ion.ucl.ac.uk/spm/), MATLAB R2017b (Mathworks Inc. Sherborn, MA), and the Conn toolbox (version 17f; https://www.nitrc.org/projects/conn; RRID: SCR_009550; Whitfield-Gabrieli & Nieto-Castanon, 2012). The preprocessing consisted of realignment, unwrapping, slice-timing correction, normalization to Montreal Neurological Institute (MNI) space, and smoothing with an 8-mm full-width at half-maximum Gaussian kernel. Then, we performed denoising with multiple regression to remove noise related to body movement and non-neural physiological activities. In this step, nuisance regressors were six realign parameters and five principal components of fMRI signals from voxels corresponding to white matter and cerebrospinal fluid made by CompCor (Behzadi et al., 2007). We also applied scrubbing to the data to remove outliers resulting from head movements (Power et al., 2014). Subsequently, we used a band-pass filter (0.008 < f < 0.09 Hz) to remove the remaining noises from fMRI signals.

In each participant, FC maps were calculated using seed-based correlation analysis. The seed regions of this study were as follows: the anterior cingulate cortex (ACC), PCC, mPFC, anterior insular cortex (aINS), sensorimotor cortex, corresponding to the lateral part of the sensorimotor network, amygdala (AMG), and nucleus accumbens (NAc). In previous studies, these regions are thought to be related to pain in FM and EIH. The seed templates of these regions were predefined and built into the Conn toolbox. In addition to the FC analysis, we performed amplitude of low-frequency fluctuations (ALFF) (Yang et al., 2007), fractional ALFF (fALFF) (Zou et al., 2008), and local correlation (LCOR) (Deshpande et al., 2009) analysis to investigate spontaneous brain activity.

2.4. Statistics

For the comparison in clinical indices and motor abilities before and after the 3-week exercise therapy, we performed paired t-tests with significance level of 0.05. In addition, the Bonferroni correction was applied in each statistical comparison for clinical indices (the number of comparisons was eight) and motor abilities (that was seven).

For the second-level analysis for ALFF, fALFF, LCOR, and FC, the threshold at the voxel level was set at uncorrected p < 0.001, and the cluster level threshold was set at false discovery rate (FDR)-corrected p

Table 2

Clinical and motor ability indices before and after exercise therapy.

Index name	Before ET (Mean ± S.D.)	After ET (Mean ± S.D.)	P value
Clinical indices			
JFIQ	63.5 ± 19.5	50.5 ± 21.0	0.001858*
PDAS	28.8 ± 14.8	20.6 ± 15.8	0.020507
HADS Anxiety	7.8 ± 5.2	6.1 ± 4.3	0.003056*
HADS Depression	7.6 ± 3.2	4.5 ± 3.5	0.000904*
PCS	30.5 ± 10.4	27.8 ± 13.8	0.219374
EQ-5D-3L	0.503 ± 0.177	0.597 ± 0.144	0.024169
PSEQ	25.8 ± 13.6	28.6 ± 14.3	0.220170
AIS	11.8 ± 4.5	9.6 ± 4.3	0.094338
Motor ability			
Walking speed (m/s)	0.97 ± 0.48	1.28 ± 0.46	0.000340†
Cadence (step/s)	1.8 ± 0.5	2.0 ± 0.5	0.001209†
Stride (m)	1.04 ± 0.36	1.23 ± 0.32	0.003060†
Daily step counts	3885.5 ± 2528.5	5900.9 ± 3488.5	0.001745†
One-leg standing time (s; up to 60 s)	24.8 ± 25.5	28.3 ± 25.2	0.004155†
Ergometer cycling intensity (watts)	23.6 ± 13.3	34.8 ± 13.5	0.002532†
Ergometer cycling time (s)	10.9 ± 7.6	18.3 ± 9.1	0.000268†

ET = exercise therapy; JFIQ = Japanese version of the Fibromyalgia Impact Questionnaire; PDAS = Pain Disability Assessment Scale; HADS = Hospital Anxiety and Depression Scale; PCS = Pain Catastrophizing Scale, PSEQ = Pain Self-Efficacy Questionnaire; AIS = Athens Insomnia Scale. Asterisks (*) mean statistically significant after the Bonferroni correction (since it was below 0.00625 = 0.05/8). Daggers (†) mean statistically significant after the Bonferroni correction (since it was below 0.00714 = 0.05/7).

< 0.05. Because statistical comparisons were conducted for the FC of 11 seed regions (mPFC, PCC, ACC, Left/Right aINS, Left/Right sensorimotor cortex, Left/Right AMG, and Left/Right NAc), we applied the Bonferroni correction to the cluster-level threshold. We also performed multiple regression analysis to explore the relationship between pre-post differences in FC and clinical and motor improvement. In this analysis, we chose JFIQ and HADS-D scores among clinical indices as covariates because the former is the index that reflects the total severity of FM symptoms, and we assumed that malfunctioning of the mesocortico-limbic system was directly linked to depression, the latter index. Moreover, we chose walking speed, daily step counts, and ergometer cycling time among the indices of motor ability as covariates for multiple regression analysis because they reflect bodily function, ADL, and exercise tolerance, respectively. For this analysis, the threshold at the voxel level was set at uncorrected p < 0.001, and the cluster level threshold was set at FDR-corrected p < 0.05. The Bonferroni correction was applied to the cluster-level threshold in each regression analysis for clinical indices (2 indices and 11 seeds) and motor abilities (3 indices and 11 seeds).

3. Results

3.1. Demographics and clinical improvement

Two patients dropped out of this study. In addition, clinical indices were lacking in the other two patients. As a result, motor ability and rs-fMRI data from 15 patients (59.5 ± 13.7 years old), and clinical indices from 13 patients (58.1 ± 15.0 years old) were analyzed. Clinical and motor ability indices are shown in Table 2. After the exercise therapy, JFIQ, HADS-A, and HADS-D significantly improved (all Ps < 0.00625 after the Bonferroni correction). Furthermore, walking speed, cadence, stride, daily step counts, one-leg standing time, ergometer cycling intensity, and ergometer cycling time, significantly improved (all Ps < 0.00714 after the Bonferroni correction).

3.2. Functional connectivity and other indices for rs-fMRI data

In paired t-tests, ALFF, fALFF, and LCOR did not show significant

Table 3
Results of multiple regression analysis for ALFF and fALFF.

Covariate	Correlation type	Cluster size (voxels)	Cluster p-value (FDR)	Peak voxel location			Brain regions
				x	y	z	
ALFF							
HADS-D	Positive	55	0.0346	18	−28	18	Right thalamus
fALFF							
JFIQ	Negative	40	0.0287	−6	40	40	Left SFG, Right SFG, Left FP

ALFF = Amplitude of Low-Frequency Fluctuations; fALFF = fractional ALFF; JFIQ = Japanese version of the Fibromyalgia Impact Questionnaire; HADS-D = Hospital Anxiety and Depression Scale Depression subscale; SFG = superior frontal gyrus; FP = frontal pole.
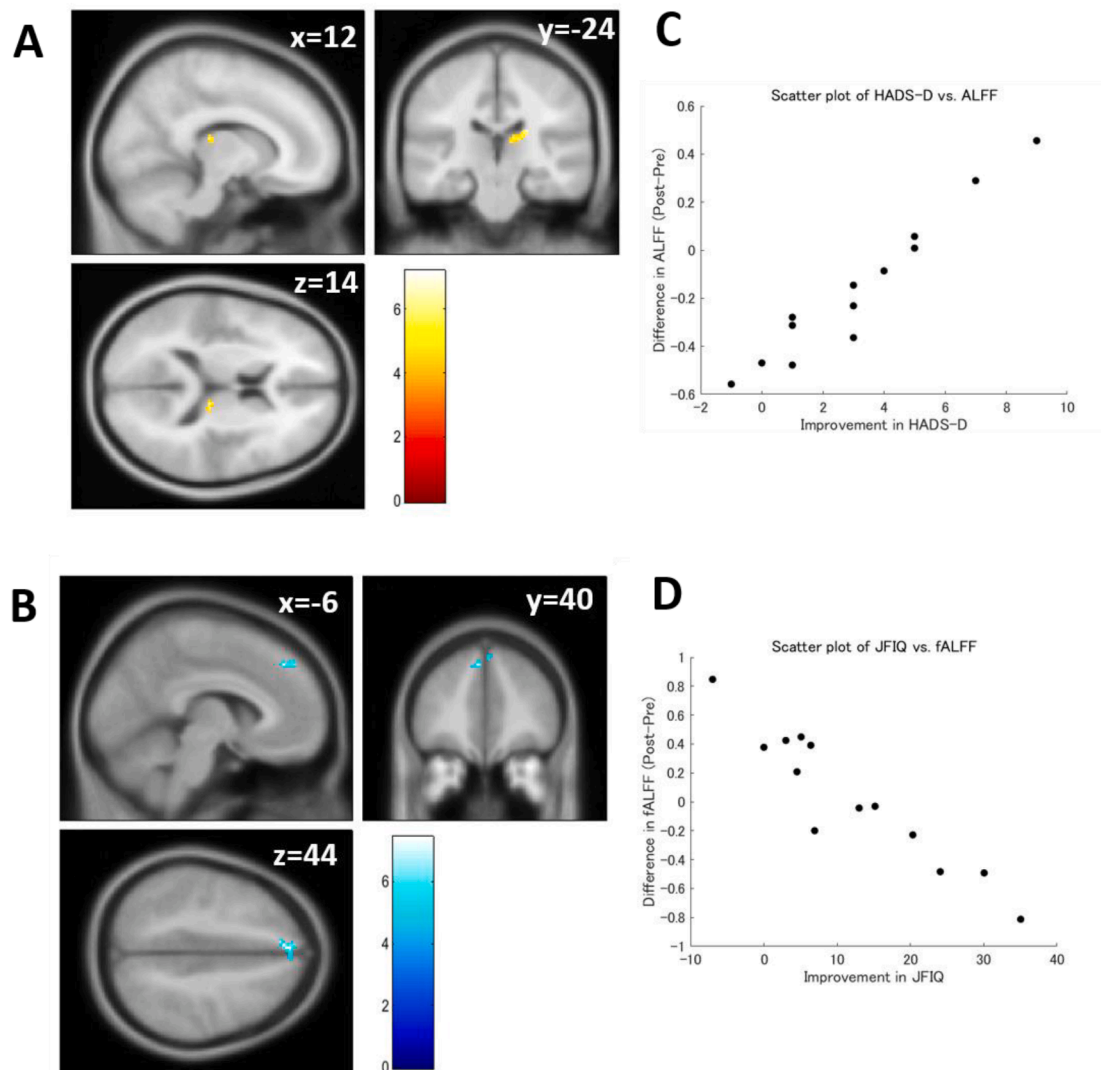

Fig. 1. Results of the multiple regression analysis for ALFF and fALFF. (A) Brain regions that showed a significant positive correlation between pre-post ALFF change and improvement of Hospital Anxiety and Depression Scale Depression subscale (HADS-D) score. (B) Brain regions that showed a significant negative correlation between pre-post fALFF change and improvement of Japanese version of the Fibromyalgia Impact Questionnaire (JFIQ) score. (C) A scatter plot of HADS-D vs. pre-post ALFF change. (D) A scatter plot of JFIQ vs. pre-post fALFF change. ALFF = Amplitude of Low-Frequency Fluctuations; fALFF = fractional ALFF.

pre-post differences. In multiple regression analyses, ALFF showed a significant negative correlation with HADS-D, and fALFF showed a significant positive correlation with JFIQ (Table 3 and Fig. 1). However, these correlations were not significant after the Bonferroni correction. LCOR was significantly correlated with neither clinical indices nor motor ability.

FC analysis showed significant FC differences before and after the 3-week exercise therapy (Table 4 and Fig. 2). FC between the ACC and operculum regions significantly decreased after exercise therapy. FC of the left sensorimotor cortex with the caudate nucleus significantly increased, and that with the aINS decreased after exercise therapy. These pre-post differences were statistically significant even after applying the Bonferroni correction for the cluster-level threshold, except for FC between the left sensorimotor cortex and aINS.

Multiple regression analysis revealed that differences in FC strength were significantly correlated with symptomatic improvement in patients

Table 4
Results of paired *t*-test for functional connectivity.

Seed	Cluster size (voxels)	Cluster p-value (FDR)	Peak voxel location			Brain regions
			x	y	z	
Post > Pre ET						
Lateral SMN Left	219	0.00426*	24	−38	−32	Right thalamus, Right caudate
Pre > Post ET						
ACC	284	0.00104*	52	−14	20	Right CO, Right PreCG, Right PostCG, Right PO
Lateral SMN Left	205	0.00948	36	16	−2	Right IC, Right FO, Right Caudate, Right Putamen, Right Orbitofrontal gyrus

ET = exercise therapy; ACC = anterior cingulate cortex; SMN = sensorimotor network; FDR = false discovery rate; CO = central operculum; PreCG = precentral gyrus; PostCG = postcentral gyrus; PO = posterior operculum; IC = insular cortex; FO = frontal operculum. Asterisks (*) mean statistically significant after the Bonferroni correction (since it was below 0.00455 = 0.05/11).

with FM (Table 5). The pre-post difference in the JFIQ score was positively correlated with pre-post differences in ACC FC strength and right aINS FC strength (Fig. 3). The pre-post difference in the HADS-D score was also correlated with the pre-post difference in the lateral part of the sensorimotor network (SMN) (Fig. 4) and ACC. However, the correlations did not reach significance after the Bonferroni correction, except for the correlation between HADS-D and the right side of the lateral SMN FC.

Multiple regression analysis also revealed that differences in FC strength were significantly correlated with improved exercise capacity in patients with FM (Table 6). Improvement of walking speed was negatively correlated with the pre-post differences in the AMG (Fig. 5A, 5C, and 5D) and PCC FC strength. The left AMG was also positively correlated with walking speed improvement (Fig. 5B and 5F). An increase in daily step counts was negatively correlated with the pre-post differences in the right NAc (Fig. 6A and 6D) and positively correlated with the pre-post differences in the left NAc FC (Fig. 6B and 6E) and the left aINS FC strength (Fig. 6C and 6F). Ergometer cycling time improvement was positively correlated with the pre-post difference in the right AMG (Fig. 7C and 7F), mPFC, PCC (Fig. 7A and 7D), and ACC FC strength and negatively correlated with the pre-post difference in PCC (Fig. 7B and 7E) and the left aINS FC strength. The correlations between walking speed and right AMG FC, daily step counts and left aINS FC, and ergometer cycling time and PCC FC were still significant even after the Bonferroni correction.

4. Discussion

In this study, we examined the effect of the 3-week exercise therapy on FM and its neural basis using rs-fMRI and functional connectivity analysis. We found that our 3-week exercise therapy improved not only motor abilities but also several clinical symptoms of patients with FM. Moreover, the degrees of improvement in those indices were significantly correlated with the pre-post differences in FC of brain regions that are considered to be related to pain chronification, including the NAc and AMG. These results indicate that exercise therapy can ameliorate symptoms of FM, and they suggest that its effect results from functional alterations of the brain, including the mesocortico-limbic system.

4.1. Effect of the 3-week exercise therapy on symptoms of FM

Our 3-week exercise therapy was able to improve not only motor abilities but also symptoms of FM. In particular, exercise therapy significantly improved depression and anxiety in patients with FM, suggesting that exercise therapy normalizes the aberrant functioning of the mesocortico-limbic system.

The mesocortico-limbic system consists of the reward system, AMG, hippocampus, and mPFC (Klein et al., 2019). Under chronic pain or chronic stress condition, the reward system is suppressed, and the AMG in excessive excitability due to fear and anxiety suppresses mPFC and NAc activities (Radley, 2012). In previous animal studies, two weeks of voluntary wheel running decreased pain behavior in partial sciatic nerve ligation (PSL) model mice, which is accompanied by activation of dopamine neurons in the ventral tegmental area (VTA) projecting to the NAc (brain reward system) (Kami et al., 2018). Moreover, the voluntary running activated the basomedial amygdala neurons that project to the NAc to promote goal-directed behavior (Kami et al., 2020), while it suppressed gamma-aminobutyric acidergic neurons in the central AMG, an output nucleus of the AMG, to reduce fear response to painful stimuli (Kami et al., 2020). It has been reported that the mesocortico-limbic system of patients or animals suffering chronic pain is malfunctioning (Baliki et al., 2010, 2012; Vachon-Presseau et al., 2016). Especially, the activity of the NAc is depressed (Ji et al., 2010; Lee et al., 2015). As the findings of animal studies have indicated (Kami et al., 2018, 2020), exercise may activate the reward system and normalize the function of the mesocortico-limbic system, the center of which is the NAc. Moreover, exercise enables us to take positive, goal-directed behavior, while suppressing negative fear response, such as freezing (immobility). Our result suggests that the same mechanism acts in patients with FM.

4.2. Pre-post differences in functional connectivity

In this study, FC analysis revealed that the sensorimotor cortex and ACC changed their functional relations after the 3-week exercise therapy. FC between the left sensorimotor cortex and right thalamus after exercise therapy was stronger than those before the exercise therapy. In contrast, FC between the left sensorimotor cortex and the right aINS before exercise therapy was stronger than those after exercise therapy. In addition, FC between the ACC and the ventral part of the right sensorimotor cortex before exercise therapy was stronger than those after exercise therapy. Interestingly, the strengths of these FC after exercise therapy were around zero, suggesting that exercise therapy normalized aberrant FC alterations in patients with FM.

FC that showed significant pre-post differences mainly consisted of the SMN, that is, the sensorimotor cortex, and the salience network, in particular, the ACC and the aINS. These networks correspond to the lateral and medial systems of the pain matrix, respectively. It is thought that the former has a role in processing the sensory aspect of pain and the latter in processing the affective aspect of pain (Ingvar, 1999; Brooks & Tracey, 2005). These regions were reported to show higher responsiveness to experimental pain stimuli in patients with FM (Gracely et al., 2002). These two networks are functionally connected in healthy adults, although their spatial patterns are highly heterogeneous (Hegarty et al., 2020). In patients with chronic pain, FC strength between the sensorimotor cortex and insula was increased compared to healthy controls (Kutch et al., 2017). Moreover, patients with low back pain showed that the salience network had stronger functional connections to a specific area in the primary somatosensory cortex representing the back than healthy controls. This functional connection was strengthened by the maneuvers exacerbating pain (Kim et al., 2019). In contrast to low back pain, pain in FM occurs all over the body. Therefore, the FC of the salience network is probably uniform across the sensorimotor cortices in patients with FM.

Although functional connections between the SMN and the salience network changed after the 3-week exercise therapy, those changes did
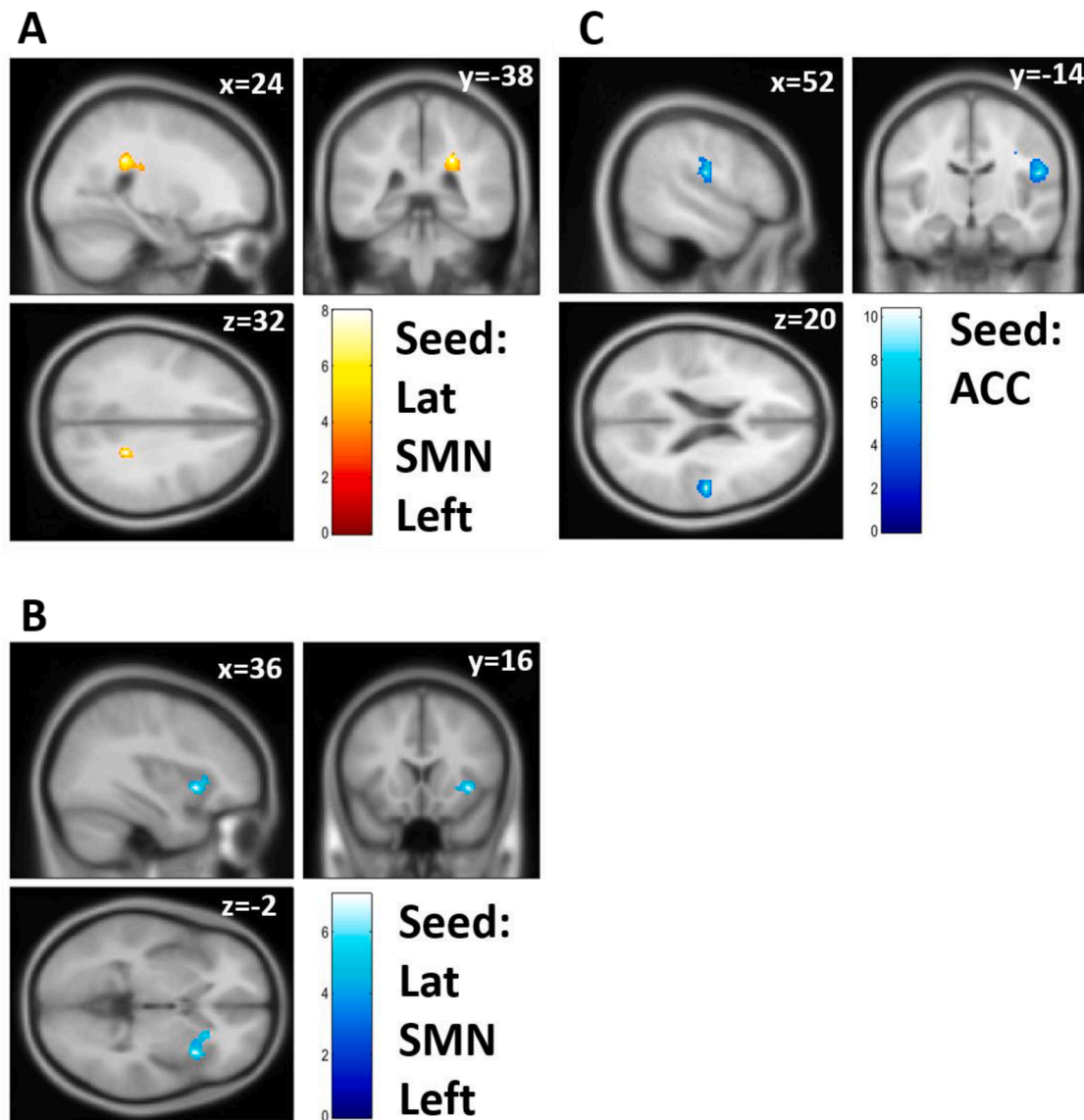
Fig. 2. Functional connectivity (FC) showed a significant difference between pre- and post-exercise therapy. (A) FC between the left lateral part of the sensorimotor network (SMN) and the right caudate/thalamus after the exercise therapy was stronger than that before the exercise therapy. (B) FC between the left lateral part of the SMN and the right anterior insula was weaker after the exercise therapy than before. (C) FC between the ACC and right operculum was weaker than before the exercise therapy. Lat = lateral; SMN = sensorimotor network; ACC = anterior cingulate cortex.

Table 5
Results of multiple regression analyses for functional connectivity.

Covariate	Seed	Correlation type	Cluster size (voxels)	Cluster p-value (FDR)	Peak voxel location			Brain regions
					x	y	z	
JFIQ	ACC	Positive	188	0.00548	64	−36	26	Right SMG, Right PT, Right PO
	Right aINS	Positive	155	0.02736	−56	16	4	Left IFG, Left PreCG
HADS-D	Lateral SMN Left	Positive	166	0.00827	28	8	34	Right MFG
	Lateral SMN Right	Negative	252	0.000781*	24	−78	0	Right OFusG, Right iLOC
	ACC	Positive	149	0.018912	28	32	−10	Right FOrb, Right FP, Right IC
			126	0.019591	−62	−54	−18	Left toITG
		Negative	120	0.039719	30	64	16	Right FP

JFIQ = Japanese version of the Fibromyalgia Impact Questionnaire; HADS-D = Hospital Anxiety and Depression Scale Depression Subscale; ACC = anterior cingulate cortex; SMN = sensorimotor network; SMG = supramarginal gyrus; PT = planum temporale; PO = posterior operculum; IFG = inferior frontal gyrus; PreCG = precentral gyrus; MFG = middle frontal gyrus; OFusG = occipital fusiform gyrus; iLOC = inferior lateral occipital cortex; FOrb = orbitofrontal gyrus; FP = frontal pole; IC = insular cortex; toITG = temporooccipital part of inferior temporal gyrus. An asterisk (*) means statistically significant after the Bonferroni correction (since it was below 0.00227 = 0.05/22).
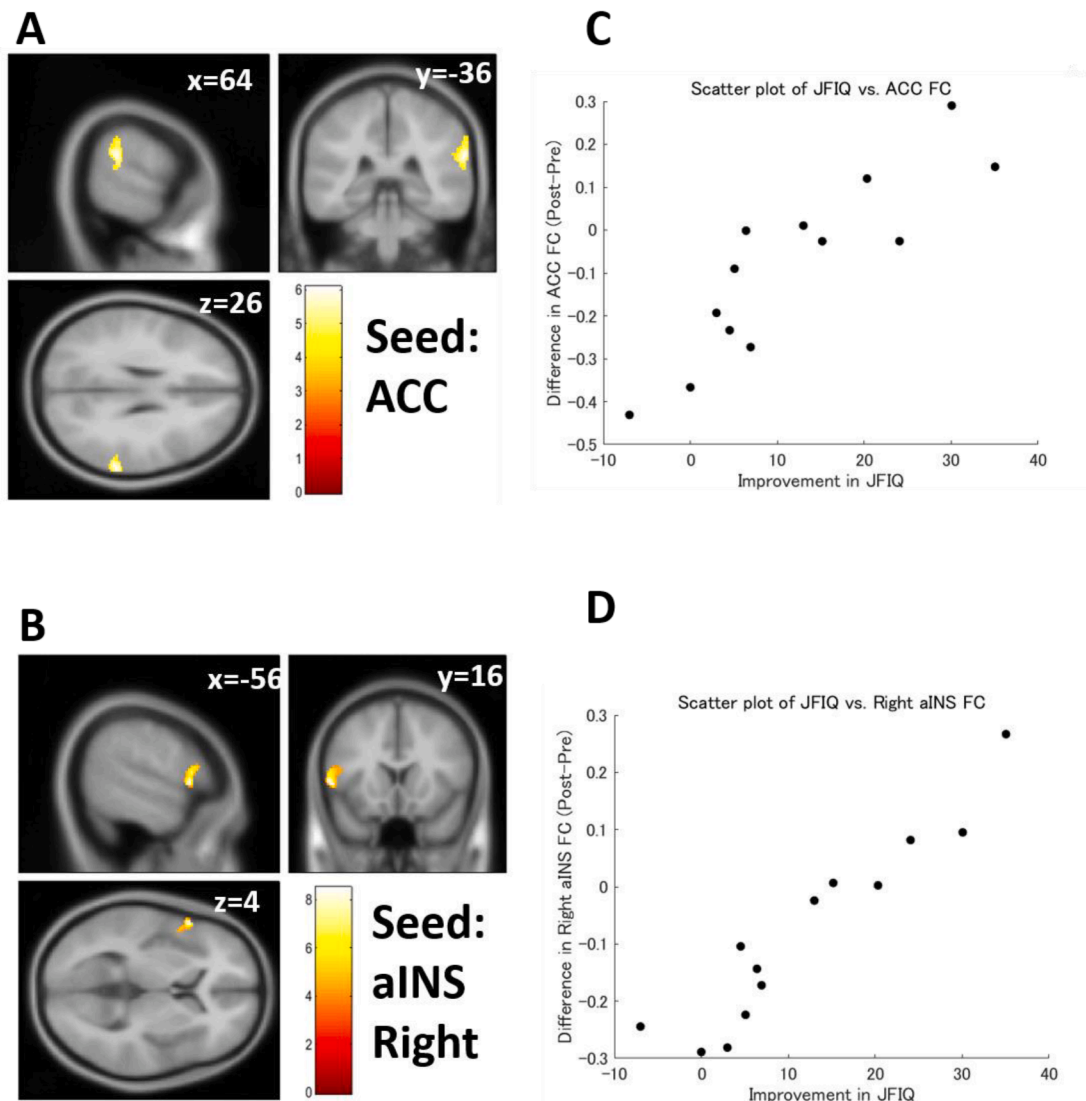
Fig. 3. Functional connectivity (FC) correlated with Japanese version of the Fibromyalgia Impact Questionnaire (JFIQ) score. (A) FC between the anterior cingulate cortex (ACC) and the right supramarginal gyrus showed a significant positive correlation with the JFIQ score. (B) FC between right anterior insula (aINS) and the left inferior frontal gyrus/precentral gyrus also showed a significant positive correlation with the JFIQ score. (C) A scatter plot of JFIQ score vs. FC of the ACC. (D) A scatter plot of JFIQ score vs. FC of the right aINS. Color bars indicate t-values.

not directly link to improved clinical symptoms or motor abilities. It is unclear how SMN-salience network FC change is involved in symptomatic improvement by exercise therapy in patients with FM. Therefore, it is necessary to investigate this issue in future studies.

Relationship between changes in functional connectivity and improvement of clinical symptoms and motor abilities after the 3-week exercise therapy for patients with FM

Changes in FC strength of sensorimotor cortices, aINS and ACC were related to improved FM symptoms. In particular, FC strength between the right sensorimotor cortex and the fusiform gyrus was negatively correlated with the improvement of HADS-D. Although these regions are not generally considered to be related to depression, a previous study reported hypoconnectivity between the fusiform gyrus and sensorimotor areas in patients with major depressive disorder (Chen et al., 2021). Furthermore, a gray matter volume decrease (Shi et al., 2016) and abnormal dopamine function (Albrecht et al., 2016) in this area were previously reported in patients with FM. The fusiform gyrus is involved in emotional regulation (Fonville et al., 2013; Harry et al., 2013). Taken together, this finding can shed light on the involvement of the fusiform

gyrus in the depressive symptoms of patients with FM.

In contrast to FM symptoms, changes in FC strength of the mesocortico-limbic system, such as the ACC, aINS, AMG, and NAc, were related to improved motor ability. This finding suggests that exercise therapy not only directly but also indirectly improves motor ability in patients with FM via cognitive and motivational process. Although the mesocortico-limbic system (reward system; from VTA to NAc) is related to reward and motivation rather than motor function (Klein et al., 2019), the NAc projects to motor-related structures, and is thought to be involved in goal-directed behaviors (LeDoux & Daw, 2018; Namburi et al., 2015; Beyeler et al., 2016). Furthermore, as mentioned above, exercise may activate the reward system and normalize the function of the mesocortico-limbic system (Kami et al.,2020), making patients with FM take positive and goal-directed behavior. Therefore, the relationship between improved motor ability and FC changes in the mesocortico-limbic system after exercise therapy can reflect this process. This interpretation is in line with a previous finding that depression evolves in the background of pain-induced disability (Fishbain et al., 1997).

In this study, AMG-angular gyrus (AG) FC, aINS-AG/supramarginal gyrus (SMG) FC, and PCC-sensorimotor cortex FC were significantly
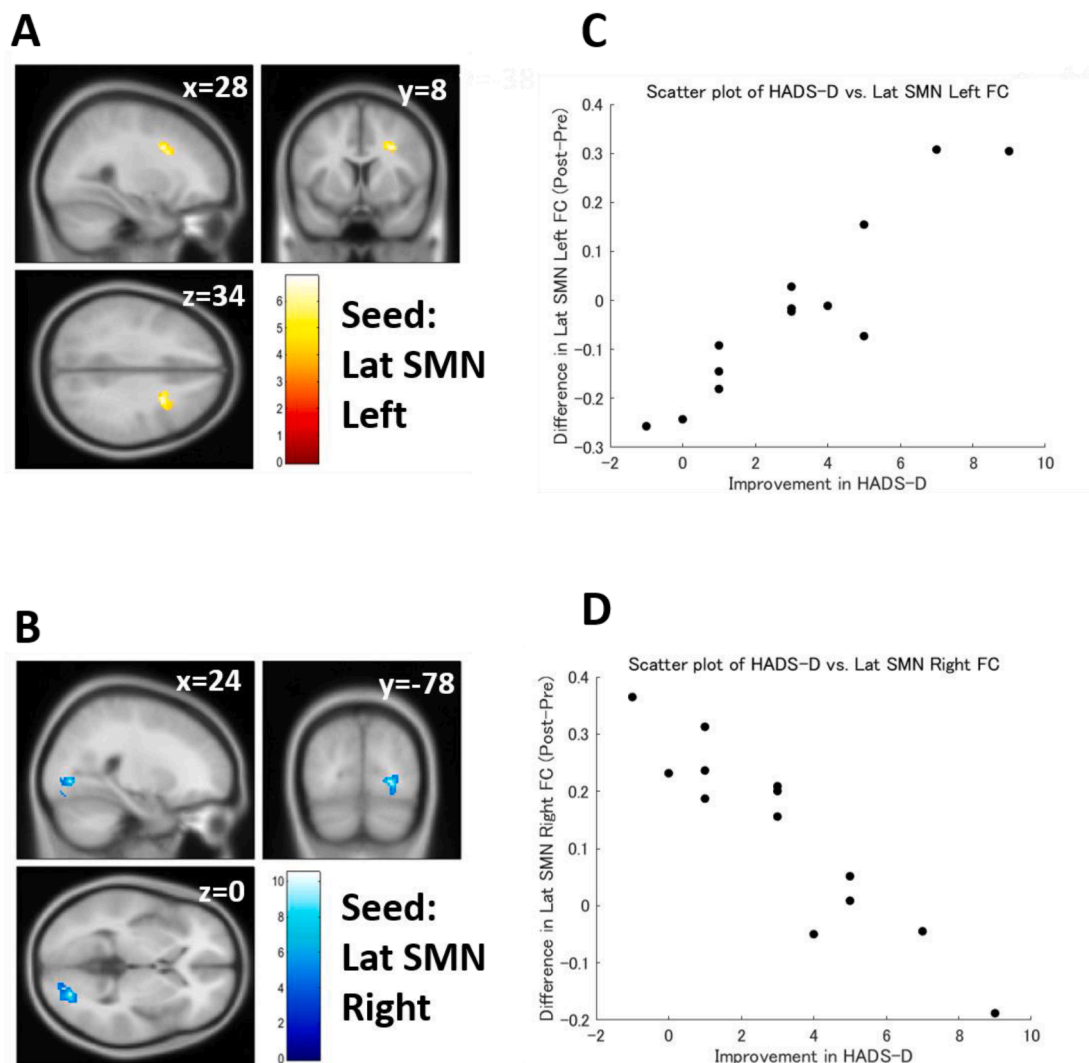
Fig. 4. Functional connectivity (FC) correlated with Hospital Anxiety and Depression Scale Depression Subscale (HADS-D) score. (A) FC between the left lateral part of the sensorimotor network (SMN) and middle frontal gyrus showed a significant positive correlation with the HADS-D score. (B) FC between the right lateral part of the SMN and the right occipital fusiform gyrus showed a significant negative correlation with the HADS-D score. (C) A scatter plot of HADS-D score vs. FC of the left lateral part of SMN. (D) A scatter plot of HADS-D score vs. FC of the right lateral part of SMN. Lat = lateral; Color bars indicate t-values.

correlated to the improvement of motor abilities by the 3-week exercise therapy. However, as mentioned above, these FC are less likely to be directly involved in motor function except for the sensorimotor cortex. On the other hand, these regions have been thought to be related to the development and maintenance of chronic pain (Yang et al., 2019). The AMG is known to have a critical role in emotion (Šimić et al., 2021). A previous meta-analysis revealed that pain with concomitant depression was associated with the right AMG (Zheng et al., 2022). The angular gyrus has a role in integrating multimodal sensory information (Seghier, 2013), and this region is considered a part of the default mode network (DMN) (Raichle, 2015). Although studies showing that AMG-AG FC is directly related to pain processing are scarce, several studies pointed out that this FC is involved in the regulation of emotions. For example, a previous study reported that gray matter volumes of the AMG and AG in patients with mild cognitive impairment were significantly correlated with their financial capacity (Giannouli & Tsolaki, 2019). The authors interpreted that this result suggested the importance of emotion regulation in a financial capacity. Another study reported that AMG-AG FC was increased by imagined music performance (Tanaka & Kirino, 2021), suggesting that this FC is related to emotion regulation, because music evokes emotion. Moreover, a previous study reported that music listening decreased pain intensity and spontaneous AG activity in

patients with FM, and they were significantly correlated (Garza-Villar-real et al., 2015). As with this study, our 3-week exercise therapy could improve motor ability and FM symptoms via normalization of emotion regulation system.

The aINS is known to be a part of the salience network (Seeley, 2019). The inferior parietal lobule, including the AG and SMG, is known to be a part of the default mode network (Raichle, 2015). The aberrant functional interaction between them has been reported in patients with FM. DMN-aINS FC strength was correlated to pain intensity in patients with FM (Napadow et al., 2010; Ichesco et al., 2014; Čeko et al., 2020), and Pregabalin administration decreased DMN-aINS FC (Harris et al., 2013). Moreover, a previous study reported that pre-treatment aINS-AG FC was significantly correlated with the pre-post difference in pain severity (Argaman et al., 2022). Taken together, the aINS-AG/SMG FC change by the exercise therapy could be a part of the underlying mechanism of exercise-induced improvement of FM symptoms.

PCC is one of the central regions of the DMN (Raichle, 2015). The sensorimotor cortex is a part of the SMN (Smith et al., 2009). These two regions receive sensory information from the thalamus. Previous studies have reported PCC FC alteration in patients with chronic pain (Cifre, 2012; Duke Han et al., 2013; Kucyi et al., 2014; Hemington et al., 2016). In patients with acquired upper limb amputation, FC between the DMN

Table 6

Results of multiple regression analyses for functional connectivity.

Covariate	Seed	Correlation type	Cluster size (voxels)	Cluster p-value (FDR)	Peak voxel location			Brain regions
					x	y	z	
Walking speed	Right AMG	Negative	341	0.000327*	−32	−60	34	Left sLOC, Left AG
			245	0.001808	−40	10	36	Left MFG, Left PreCG
			220	0.002368	−66	−26	−2	Left pMTG, Left pSTG
			175	0.005284	−34	6	60	Left MFG
			174	0.005284	34	−64	−40	Cerebellum
			130	0.016959	68	−24	−14	Right pMTG, Right toMTG
			126	0.016959	−22	20	−16	Left Orbitofrontal gyrus
			115	0.021478	56	−58	46	Right AG, Right sLOC
	Left AMG	Positive	223	0.002073	−4	−50	74	Right PostCG, Left PostCG, Left SPL, Precuneus, Right PreCG, Left PreCG, Right SPL
		Negative	147	0.04921	−26	24	−16	Left orbitofrontal gyrus
Daily step counts	Right NAc	Negative	196	0.004006	2	−2	56	Right SMA, Left SMA, Right PreCG, Left PreCG
			186	0.004006	−38	14	6	Left FO, Left IC, Left FOrb
	Left NAc	Positive	115	0.048617	16	−52	22	Precuneus
	Left AMG	Negative	142	0.025791	−66	−32	−12	Left pMTG
			111	0.029456	−24	14	−20	Left orbitofrontal gyrus, Left TP, Left IC
			106	0.029456	−32	32	−12	Left orbitofrontal gyrus, Left FP
	ACC	Positive	185	0.007309	−16	−32	−8	Brainstem, PC, Left pPaHC, Hipp, Thalamus, Cerebellum, Right pPaHC
	Left aINS	Positive	229	0.001069*	44	−44	30	Right AG, Right pSMG
Ergometer cycling time	Right AMG	Positive	188	0.006603	26	24	42	Right MFG, Right SFG, Right FP
			182	0.006603	44	−74	32	Right sLOC, Right AG
	mPFC	Positive	222	0.004757	34	−66	−40	Cerebellum
	PCC	Positive	204	0.006302	26	−98	16	Right OP
		Negative	356	0.000062*	18	−52	72	Right SPL, Precuneus, Left PostCG, Right PostCG, Right sLOC, Left PreCG
	ACC	Positive	216	0.004057	10	−90	4	Right OP, Right ICC, Right LG
			135	0.020982	−24	44	−2	mPFC
	Left aINS	Negative	143	0.017686	−48	−82	−2	Left iLOC

sLOC = superior lateral occipital cortex; AG = angular gyrus; MFG = middle frontal gyrus; PreCG = precentral gyrus; pMTG = posterior part of middle temporal gyrus; toMTG = temporooccipital part of middle temporal gyrus; PostCG = postcentral gyrus; SPL = superior parietal lobule; SMA = supplementary motor area; FO = frontal operculum; IC = insular cortex; FOrb = orbitofrontal gyrus; TP = temporal pole; FP = frontal pole; pPaHC = posterior part of parahippocampal cortex; Hipp = hippocampus; pSMG = posterior supramarginal gyrus; SFG = superior frontal gyrus; OP = occipital pole; ICC = intracalcarine cortex; LG = lingual gyrus. Asterisks (*) mean statistically significant after the Bonferroni correction (since it was below 0.001515 = 0.05/33).

and missing hand region in the SI increased compared to healthy controls (Makin et al., 2015). Furthermore, in patients with chronic low back pain, the increase in pain intensity by specific maneuvers was related to the change in FC strength between the DMN and the primary somatosensory cortex (Kim et al., 2019). Patients with comorbid migraine and insomnia showed increased PCC-precentral gyrus FC compared to healthy controls (Chou et al., 2021). Patients with FM experience sleep disturbance (Harding, 1998), and pain is closely related to insomnia (Affleck et al., 1996). Moreover, a previous study revealed that insomnia causes hyperalgesia and physical inactivity, which may lead to depression (Bigatti et al., 2008). Although not statistically significant, patients tended to improve their insomnia in the present study. Therefore, considering these previous findings, the relationship between the pre-post difference in PCC-sensorimotor cortex FC and the improvement of ergometer cycling time suggests that our 3-week exercise therapy improved sleep quality and physical performance, which in turn lead to improved FM symptoms.

As mentioned above, we found that FC of several brain regions was related to improvement of FM symptoms and motor ability. However, they did not show significant differences in their strengths before and after the exercise therapy. It suggests that FC change among certain brain regions is critical to the improvement of FM symptoms and motor ability in patients with FM even though FC change induced by the exercise therapy is too small to detect in a pre-post comparison. Moreover, as we hypothesized, brain regions related to emotion or reward processing comprised FC related to clinical improvement in patients with FM. Of course, there is another possibility that slight FC change occurred

secondarily from the improvement of FM symptoms and motor ability induced by the exercise therapy. Our study cannot distinguish them due to methodological limitations. To test those possibilities, further studies with larger sample size to perform statistical analysis for evaluating causal relationship or interventions manipulating directly FC strength are necessary.

Limitations

We should consider several limitations in this study. Firstly, the sample size of this study was small. In recent years, it has been revealed that FC strength is unstable (Noble et al., 2017), and the influences of diseases on FC are less than expected (Yamashita et al., 2019). Thus, results obtained from studies with a small sample size are vulnerable, and the power of tests is low. Therefore, results and the subsequently derived interpretations should be taken with caution. However, to our knowledge, only one study has investigated the neural mechanisms underlying exercise therapy in FM patients so far. Therefore, we are confident that our study is meaningful and valuable. In the future, conducting clinical studies with a larger sample size is necessary. Secondly, the lack of any control groups is also a critical limitation of this study. Therefore, we cannot conclude in this study that exercise therapy caused changes in brain function and improved symptoms and physical performance. Clinical randomized trials are necessary to confirm the effect of exercise therapy on symptoms and brain activities in patients with FM. Thirdly, our results do not indicate any causal relationship between FC strength and FM symptoms. As widely accepted/recognized,
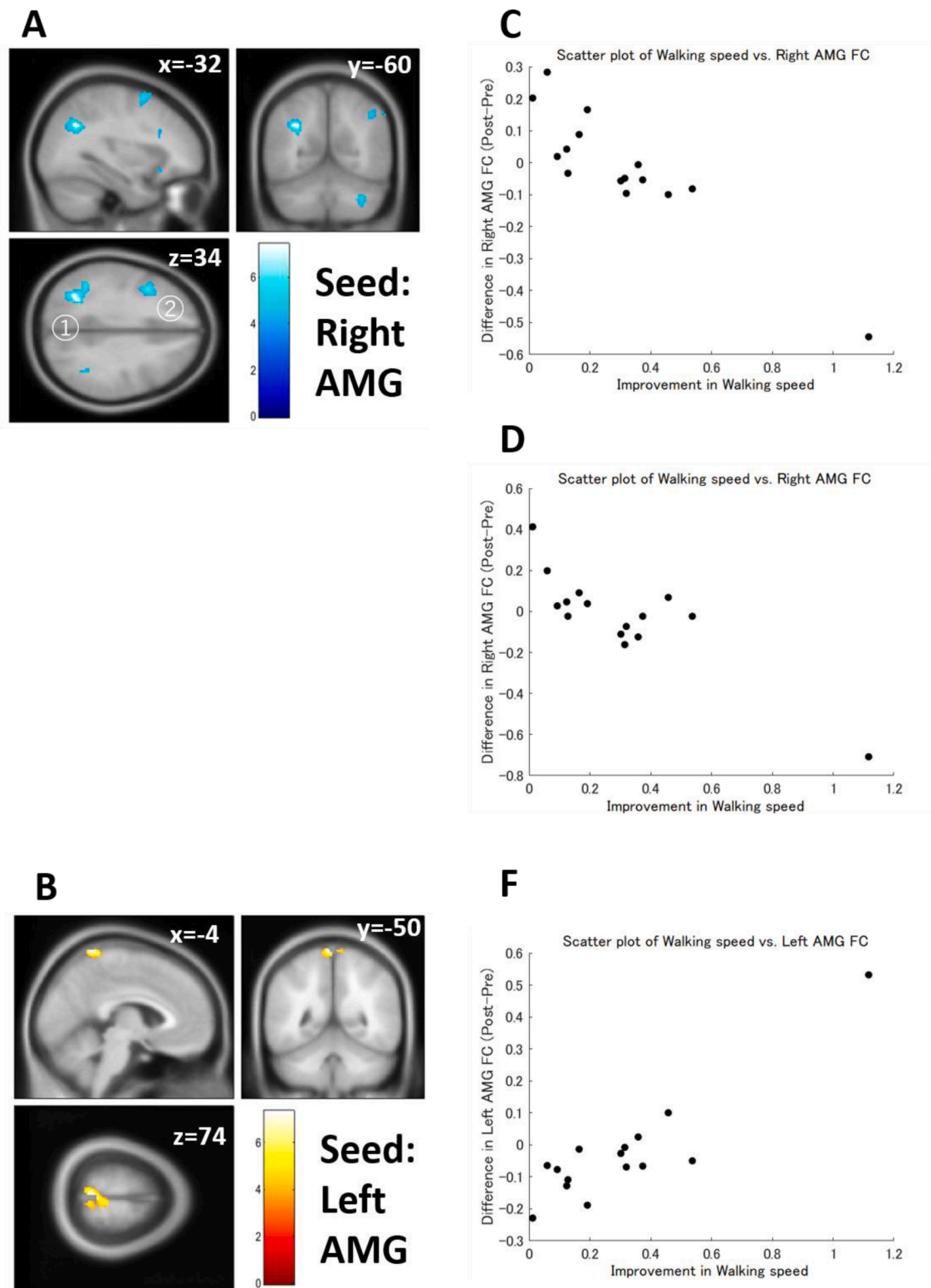
Fig. 5. Functional connectivity (FC) correlated with walking speed. (A) FC between the right amygdala (AMG) and the left lateral occipital cortex (LOC) (A①) or the left middle frontal gyrus (MFG) (A②) showed a significant negative correlation with walking speed. (B) FC between the left AMG and the postcentral gyrus showed a significant positive correlation with walking speed. (C) A scatter plot of walking speed vs. the right AMG-LOC FC. (D) A scatter plot of walking speed vs. the right AMG-MFG FC. (F) A scatter plot of walking speed vs. the left AMG FC. Color bars indicate t-values.

correlations do not ensure the presence of causal relationships. Therefore, we cannot conclude any causal relationship between exercise therapy, FM symptoms, and FC strength. To fully understand the underlying mechanisms of exercise therapy on FM symptoms and spontaneous brain activity, statistical approaches that can evaluate the causal relationship, such as structural equation modeling, should be applied. Finally, we did not examine how long the effect of the 3-week exercise therapy lasts in this study. Our study was able to demonstrate
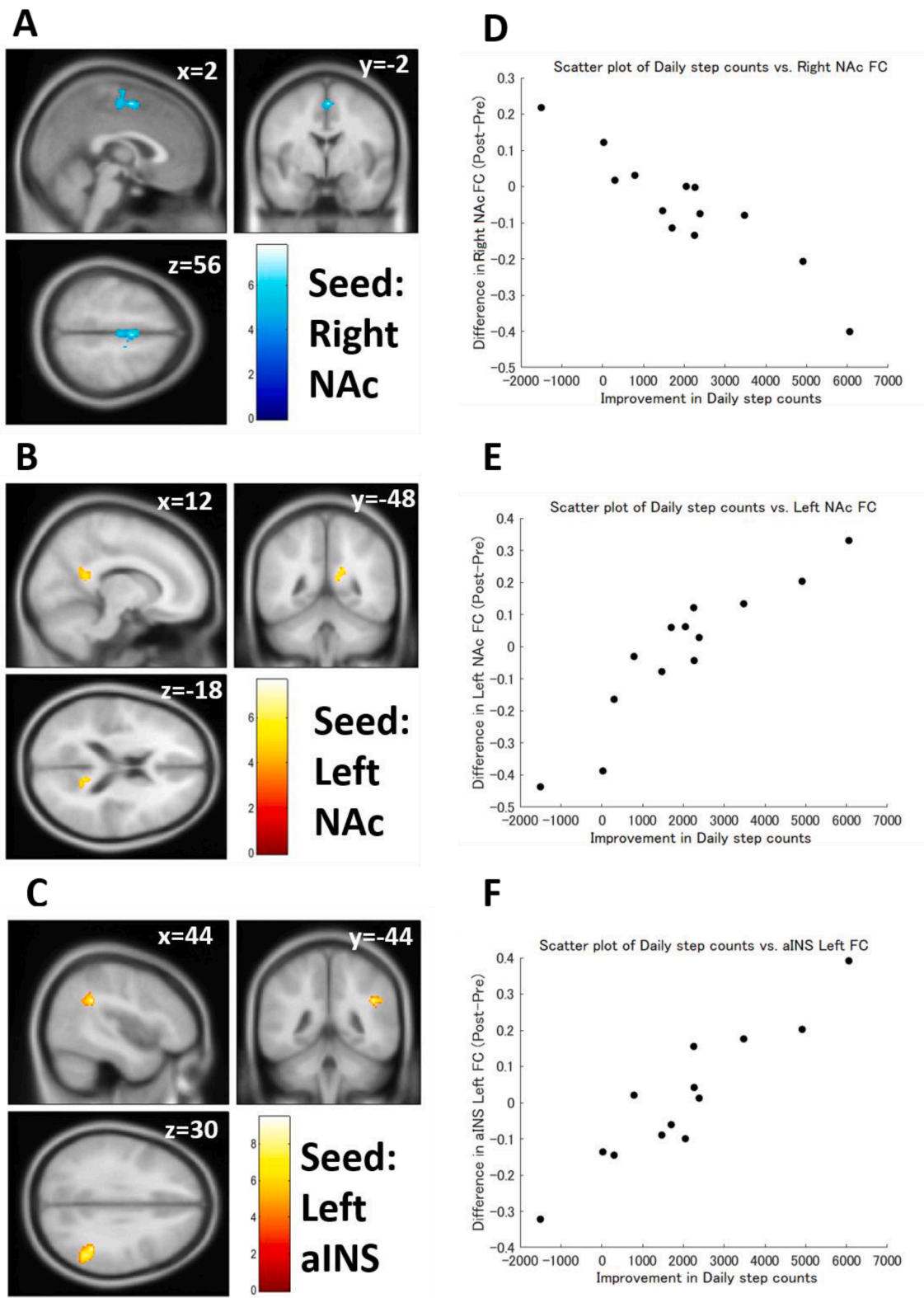
Fig. 6. Functional connectivity (FC) correlated with daily step counts. (A) FC between the right nucleus accumbens (NAc) and the supplementary motor area/ precentral gyrus showed a significant negative correlation with daily step counts. (B) FC between the left NAc and the precuneus showed a significant positive correlation with daily step counts. (C) FC between the left anterior insula (aINS) and the supramarginal gyrus showed a significant positive correlation with daily step counts. (D) A scatter plot of daily step counts vs. the right NAc FC. (E) A scatter plot of daily step counts vs. the left NAc FC. (F) A scatter plot of daily step counts vs. the left aINS FC. Color bars indicate t-values.

Fig. 7. Functional connectivity (FC) correlated with ergometer cycling time. (A) FC between the posterior cingulate cortex (PCC) and the occipital pole showed a significant positive correlation with ergometer cycling time. (B) FC between the PCC and the precuneus showed a significant negative correlation with ergometer cycling time. (C) FC between the right amygdala (AMG) and the middle frontal gyrus showed a significant positive correlation with ergometr cycling time. (D) A scatter plot of the ergometer cycling time vs. the PCC - occipital pole FC. (E) A scatter plot of the ergometer cycling time vs. the PCC - precuneus FC. (F) A scatter plot of the ergometer cycling time vs. the right AMG FC. Color bars indicate t-values.

that the 3-week exercise therapy alleviated symptoms of FM. However, we did not examine how long this effect will last. If exercise therapy is widely applied in clinical practice to treat patients with FM, this point should be examined in future studies.

Conclusion

Using rs-fMRI and FC analysis, we examined whether our 3-week exercise therapy can improve FM symptoms and what FC changes exercise therapy causes in patients with FM. Patients with FM showed significant improvement in motor abilities and clinical symptoms of FM after the 3-week exercise therapy. Moreover, pre-post differences in several FC were significantly correlated with clinical improvement of these patients, such as the general severity of FM symptoms and depression. FC changes in sensorimotor regions were related to the improvement of FM symptoms, whereas FC changes in the mesocortico-limbic system were related to improvements in motor ability. Although our findings are apparently counterintuitive, they are consistent with our hypothesis that exercise can improve the behavioral disturbance of patients with FM through functional normalization of the mesocortico-limbic system, which may lead to the improvement of FM symptoms. Although there are some limitations, our study provides intriguing evidence that the malfunctioning of the mesocortico-limbic system is involved in the development of FM, and exercise therapy can normalize the functioning of this system, changing patients' behavior in a positive way. It will in turn improve the clinical symptoms of FM.

CRediT authorship contribution statement

Shigeyuki Kan: Software, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Visualization. **Nobuko Fujita:** Methodology, Investigation, Resources, Writing – review & editing, Project administration, Funding acquisition. **Masahiko Shibata:** Writing – review & editing, Project administration. **Kenji Miki:** Investigation, Resources, Writing – review & editing. **Masao Yukioka:** Resources, Writing – review & editing. **Emiko Senba:** Conceptualization, Methodology, Writing – review & editing, Supervision.

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.

Data availability

Data will be made available on request.

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