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Two non-pharmacological interventions, amygdala and insula retraining (AIR) and physical activity, are both significantly more effective than standard medication in improving symptoms of fibromyalgia

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Abstract

Fibromyalgia (FM) involves widespread pain, fatigue, sleep disturbances, and cognitive issues, often with limited relief from medications. Non-pharmacological approaches, like Amygdala and Insula Retraining (AIR) and physical activity (PA), show promise in managing FM symptoms. This study compares the effectiveness of AIR and PA with the medication Pregabalin for improving cognitive function, sleep, pain, and depressive symptoms in FM patients. A randomized controlled study was conducted among Iranian women diagnosed with FM who were randomly allocated to one of three cohorts: (1) AIR intervention, (2) PA intervention, and (3) a control group receiving standard Pregabalin medication. Various symptoms were measured at baseline, post-intervention (12 weeks), and follow-up (8 weeks later). A series of mixed ANOVAs were used to evaluate cognitive function, sleep disturbance, pain catastrophizing, depressive symptoms, and condition symptoms (i.e., fibromyalgia impact questionnaire (FIQ). Both AIR and PA significantly improved all outcome variables compared to baseline levels and the control group. Notably, the AIR group also demonstrated significantly superior outcomes for pain catastrophizing, depressive symptoms, and overall FM impact, with large to extremely large effect sizes. This study highlights the effectiveness of non-pharmacological interventions, specifically AIR and PA, for improving cognitive function, sleep quality, pain catastrophizing, depression, and FM impact symptoms. Though a small sample size and lacking in generalizability, the study offers important and timely results, suggesting that AIR and PA may be readily accessible and helpful resources for patients, clinicians, and researchers seeking to address the often-challenging symptoms of FM.

Keywords Fibromyalgia · Sleep disorders · Cognition · Depression · Physical activity · Self-compassion · Amygdala and insula retraining (AIR)

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Introduction

Fibromyalgia (FM), a persistent condition marked by pervasive musculoskeletal pain and fatigue, predominantly affects women (Wolfe et al., 2018), with men often experiencing a milder impact and frequently remaining undiagnosed (Clauw, 2009, 2014). While the etiology of FM remains elusive, there is some evidence that it may result from a complex interplay of genetic and environmental factors, with trauma playing a significant role (Clauw, 2014). Fibromyalgia manifests in varying symptoms such as widespread pain in muscles and joints, persistent fatigue, anxiety, depression (Thieme et al., 2004), and disruptions in sleep,

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often linked to disorders like insomnia (Choy, 2015). Individuals with FM may also experience cognitive difficulties known as "brain fog" reducing concentration and memory capabilities (Ambrose et al., 2012). These symptoms can adversely affect overall well-being and significantly impact an individual's ability to engage in daily activities.

Globally, FM affects 0.2–6.6%of the population, with slightly higher rates among women (2.4–6.8%), urban dwellers (0.7–11.4%) and some individuals with disabilities (0.1–15%) (Marques et al., 2017). In Iran, prevalence is even higher, ranging from 3 to 20% (Heidari et al., 2017). Consequently, this study focused on the Iranian patient demographic.

Diagnosing FM presents challenges, requiring a comprehensive evaluation encompassing patient history, physical examination, and confirming the exclusion of conditions with similar symptoms. Although FM is a chronic condition without a cure, effective symptom relief is attainable through proper management and support. Collaborative efforts between FM patients and their healthcare providers are crucial to formulate personalized treatment plans. Treatment aims at symptom management and enhancing quality of life, typically involving a multi-faceted strategy of medications, physical therapy, psychological counseling, behavioral therapy, stress management, and lifestyle adjustments (Di Carlo et al., 2024; Kizilbash et al., 2014). While pharmacological treatments for fibromyalgia are common, they often have limited effectiveness (Bochenek et al., 2024; Häuser et al., 2014). By contrast, there is evidence that psychotherapeutic and behavioral therapies can have a positive impact on fibromyalgia symptoms. Yet, these treatment options are largely underexplored (Clauw, 2014; Hong-Baik et al., 2023).

Amygdala and Insula Retraining (AIR; known commercially as The Gupta Program), is a program designed to address chronic pain by promoting neuroplasticity. The AIR intervention utilizes "neural rewiring" brain retraining techniques developed over many years, with secondary supportive techniques such as cognitive reframing, mindfulness meditation, and guided imagery. Together, these are all aimed at modulating the central nervous system's response to pain. While the precise mechanisms of AIR remain under investigation, the foundational hypothesis posits that the intervention facilitates the formation of new neural pathways associated with pain regulation and potentially inhibit established pain pathways (Gupta, 2002, 2010; Gupta et al., in publication). This modulation could occur through various mechanisms, including strengthening the prefrontal cortex's inhibitory control over the limbic system, including the amygdala and insula (Bratty, 2024). These brain regions play a crucial role in pain processing and emotional regulation (Sanabria-Mazo et al., 2020).

Gupta's (2002, 2010, in publication) theory offers a new perspective, suggesting that fibromyalgia may be due to maladaptive neural circuits in the brain, particularly involving the amygdala and insula (Kioussis & Pachnis, 2009; Kraus et al., 2021), which are associated with pain processing and emotional regulation (Meulders, 2020). AIR is a brain retraining intervention developed in line with this theory, aiming to recalibrate these neural circuits to reduce the brain's exaggerated response to pain and stress (Steinman, 2004). Physical activity (PA) has also been shown to promote neuroplasticity and improve pain thresholds in FM patients. Together, these non-pharmacological interventions may offer a more effective symptom management strategy than standard medication (Jennings et al., 2014).

Evidence suggests that regular physical activity (PA), such as dance and exercise, also benefits FM patients, improving pain, mood, and mental health (Masquelier & D'haeyere, 2021; Norouzi et al., 2020). However, the comparative effectiveness of AIR and exercise therapy interventions for addressing FM symptoms is unknown. Therefore, the aim of the present study was to examine the effectiveness of AIR and PA versus standard pharmacological treatment on the dimensions of cognitive function, sleep disturbances, catastrophic pain, depressive symptoms, and condition symptoms among Iranian women with FM. The following hypotheses were explored.

H_1: There will be a significant improvement in participants' cognitive function, sleep disturbances, catastrophic pain, depressive symptoms, and condition symptoms after participants engage in the AIR intervention.

H_2: There will be a significant improvement in participants' cognitive function, sleep disturbances, catastrophic pain, depressive symptoms, and condition symptoms after participants engage in the physical activity intervention.

H_3: Compared to an active control group receiving medication, the two experimental groups will experience a significant improvement in participants' cognitive function, sleep disturbances, catastrophic pain, depressive symptoms, and condition symptoms after their respective AIR or physical activity interventions.

Methods

Participants

The study was conducted among Iranian women with FM. It was approved by the ethics committee of………… University………… (Ethical Approval ID: IR.KUMS.REC.1401.485) and adhered to the principles outlined in the Declaration of Helsinki ("World Medical Association

Declaration of Helsinki: ethical principles for medical research involving human subjects," 2013). Participants were recruited from local clinics, support groups, and online platforms and provided informed consent. Inclusion criteria: (1) ages 18–65 years, (2) positive FM diagnosis per the American College of Rheumatology (ACR) criteria (Katz et al., 2006; Wolfe et al., 2010), and confirmed by a rheumatologist from the Iranian National Health Service, (3) sedentary lifestyle (did not exercise regularly), from the Persian version of the short form of the International Physical Activity Questionnaire (IPAQ-SF) which was used to measure sedentary lifestyle (total days of walking ≤3) and (4) proficiency in reading and understanding Farsi. Exclusion criteria: (1) the presence of a severe Axis I psychiatric/somatic disorder, (2) an autoimmune disease, (3) the use of corticosteroid medication, or (4) participation in a concurrent randomized controlled trial (RCT).

Study design

The study was a randomized controlled trial with three points of measurement. A sample of 145 women with FM were recruited and randomly assigned to one of three cohorts, two of which were active intervention groups. The first cohort received the Amygdala and Insula Retraining (AIR) intervention. The second cohort received the physical activity (PA) program, and the third cohort (the control group) received Pregabalin medication as standard care (see Fig. 1). Importantly, participants in the AIR and PA groups that were previously on medication for FM were asked to stop taking it for the duration of the study. Participants in the control group either switched from their current medication to Pregabalin or continued with Pregabalin for the duration of the study if they were already taking it. Eighty-six participants were able to complete the study.

This study focused exclusively on women due to the higher prevalence of FM among women. Additionally, the decision to include a PA cohort necessitated a single-sex study because mixed-gender exercising is not permitted in Iran. Measurements were collected at baseline (pre-intervention), immediately after the 12-week interventions (post-test), and 8 weeks later (follow-up).

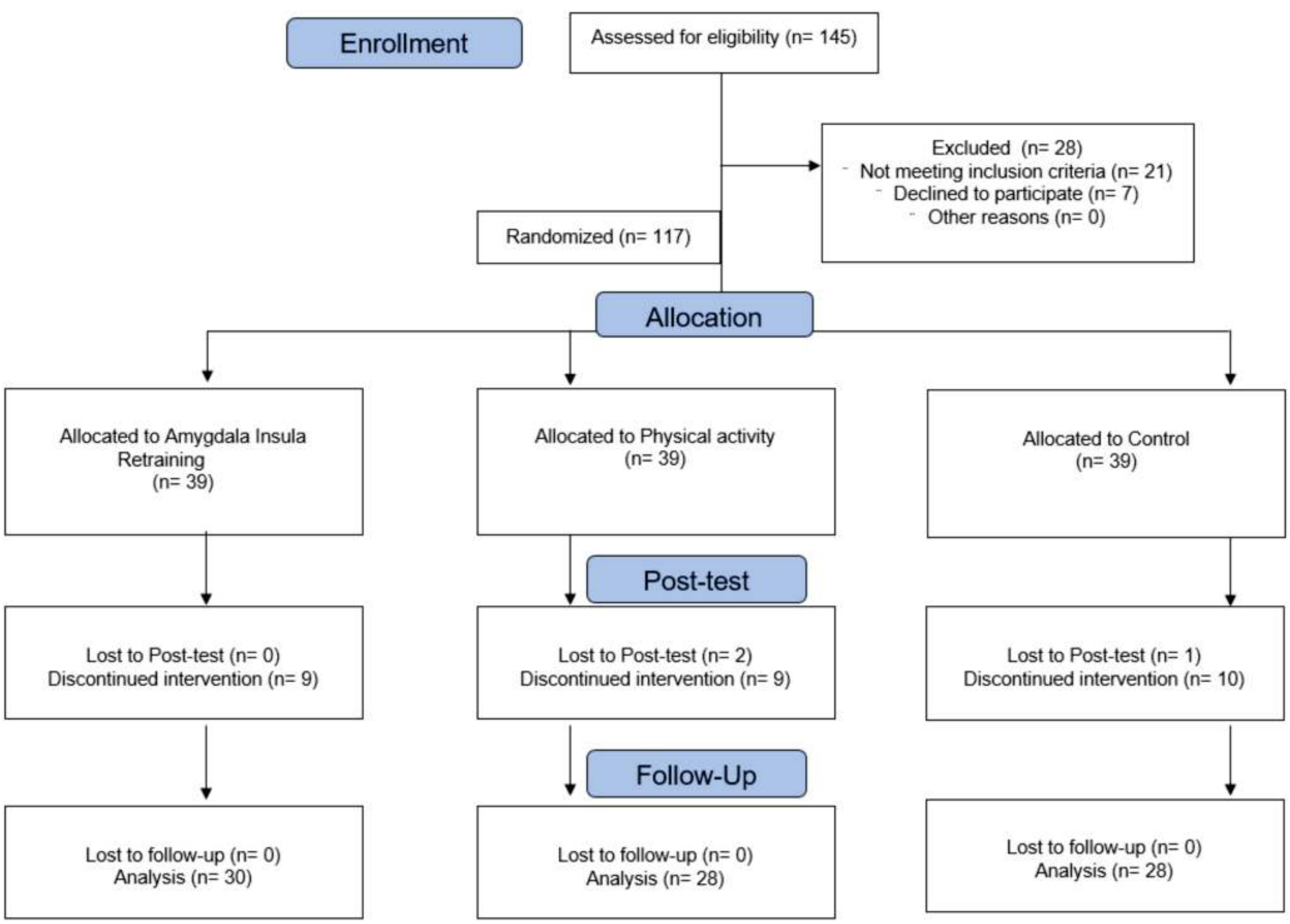

Fig. 1 CONSORT flow diagram

Interventions

Amygdala and insula retraining (AIR)

The AIR intervention includes primary neuroplasticity techniques and secondary supporting techniques such as breathing, meditation, and lifestyle therapies. The intervention was developed from a hypothesis that numerous chronic conditions, such as FM, are caused and perpetuated by brain signals that continuously and unnecessarily trigger the immune and nervous systems, as well as pain networks. This constant activation manifests as a variety of somatic symptoms, such as pain, fatigue, sleep problems, cognitive dysfunction, and many more. Consequently, the AIR neuroplasticity techniques seek to interrupt and inhibit the brain signals that activate the somatic symptoms. Further, the adverse signals are then replaced with new, neural pathways that send signals of safety to the brain and help reduce hyperactivity in the immune and nervous systems, thereby allowing the brain and body to return to homeostasis (Gupta 2002, 2010). Development of the new, neural pathways requires repetition. Therefore, practicing the neuroplasticity techniques daily for a minimum of 3 months, and preferably 6 months, is encouraged.

The AIR intervention is typically provided via a member website and digital app. It consists of 15 modules with video tutorials, audio exercises, and meditations. A printed manual of the program is mailed to participants, and community events are also offered, such as live and recorded weekly online webinars and daily experiential sessions led by an AIR-trained coach. Optional one-on-one and group coaching is also available upon demand with AIR-trained coaches.

For the purposes of this study, AIR was delivered in a slightly modified way. Participants accessed the video, audio, and meditation content via a mobile app. The printed manuals were distributed in person to participants, and in-person weekly group teaching/coaching sessions were provided (i.e., no online group sessions or one-on-one coaching). During the 60-minute weekly sessions led by two clinical psychologists familiar with AIR, participants learned how to establish a consistent breathing and meditation practice. Additionally, theoretical aspects related to FM were explored, including the AIR hypothesis, and how maladaptive immune and nervous system activity occurs and leads to adverse bodily symptoms. Participants were also encouraged to visualize good health as they prepared to learn the neuroplasticity techniques, and once they learned those main methods, they were encouraged to practice them daily.

As the 12-week intervention progressed and participants were practicing the neuroplasticity techniques, attitudes towards brain-retraining were discussed, emphasizing the importance of reducing stress and expectations, and addressing the fear of failure in recovery. Participants learned about personality traits and various lifestyle, environmental, and psychosocial factors that can affect recovery and were guided on how to address these issues. The intervention also stressed the significance of re-engaging with joy to relax the nervous system, incorporating mindfulness, and how to reintegrate to regular life (Gupta 2002, 2010).

Physical activity

The physical activity (PA) intervention was implemented through aerobic exercise, spanning a 12-week period with two 45-minute online group sessions per week (Norouzi et al., 2020). In the physical activity intervention, online classes were conducted through Zoom video conferencing platform. The exercises were led and performed by two sports coaches, each with a PhD in sports physiology. The exercises were modified according to the participants' physical fitness levels and guided by a sports coach using behavioral techniques such as goal setting. Participants engaged in dynamic aerobic exercise training while walking outdoors at an intensity estimated to reach their maximum heart rate, calculated using the '220 minus age' formula. Heart rate was monitored using an electronic pulse meter incorporated into Apple Watches. They were encouraged to keep the pace during the intervention, though they were allowed to pause individually for 1–2 min. Participants were encouraged to take an active role in monitoring and adjusting their exercise intensity based on their perceived exertion and heart rate data from their Apple Watches. This approach fostered self-regulation and promoted participant autonomy. The regimen included two components: body-weight-based core and strength training, encompassing exercises like mountain climber twist and plank with each exercise performed for 3 sets of 10–15 repetitions and with rest interval between sets (60 seconds), and dynamic aerobic exercises, involving running at 70% maximum heart rate. The sessions followed a structured format, comprising warm-up activities such as stretching and sit-ups, and concluding with a cool-down phase involving stretching and cradle movements.

Control group (pregabalin medication)

This group continued the traditional treatment for Fibromyalgia. Pregabalin was prescribed by a Rheumatology and psychiatrist in the amount of 300 to 450 mg per day (Arnold et al., 2008). In addition, participants in the control group gathered once a week in groups at the hospital, where staff asked them about their physical and psychological health, and discussed their medication and general living conditions. The patients also had group discussions among themselves about news and current events. The main purpose of these weekly gatherings was to create an in-person element of the control group design that was structurally equivalent to the two experimental groups.

Measures

Physical activity levels

Baseline physical activity levels were assessed using the Persian version of the International Physical Activity Questionnaire (IPAQ). This self-reported questionnaire assesses physical activity levels over the past 7 days, including the frequency, duration, and intensity of various activities such as walking, cycling, and moderate-to-vigorous physical activity (Vasheghani-Farahani et al., 2011). The IPAQ comprises seven questions, each rated on a 0–6 scale, with higher scores indicating higher physical activity. The Persian version of the IPAQ has demonstrated satisfactory reliability in previous research (α =0.83) and in the present study (α =0.80).

Cognitive function

Cognitive function was measured using the Integrated Cognitive Assessment (CGN_ICA), a rapid visual categorization task incorporating backward masking (Khaligh-Razavi et al., 2019). One hundred natural images, comprising 50 animals and 50 non-animal stimuli with varying difficulty levels, were presented to participants. Each image appeared for 100 milliseconds, followed by a 20-millisecond interstimulus interval (ISI), further succeeded by a dynamic noisy mask lasting 250 milliseconds. Subsequently, participants categorized the images as either animal or non-animal, by tapping the left or right side of the screen on an iPad or by pressing pre-assigned keys (‘F’ vs. ‘J’) on a RasPi keyboard. The images were centrally presented on the screen at a 7-degree visual angle. A preliminary phase involved presenting 10 introductory images (5 animal, 5 non-animal) to familiarize participants with the task, with these images excluded from the final scores. Participants who fared better than chance during the preliminary phase continued to the main task, while those performing at the level of chance or lower received further instructions and a new set of introductory images. A second round of preliminary images determined further progression to the main task or test abortion (Mirzaei et al., 2013).

Sleep disturbance

To assess sleep quality, participants completed the Farsi version (Farrahi Moghaddam et al., 2012) of the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1991). It comprises seven elements, including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, sleeping pill usage, and poor daytime functioning. Each question is graded from 0 to 3, and the scores of these seven components are combined to produce a total score ranging from 0 to 21. The higher the score the poorer quality of sleep, with a score of 6 or more indicating poor sleep quality. Reliability of the Persian version of the PSQI was satisfactory in prior research (α =0.78). In the present study, reliability was also acceptable (α =0.81).

Pain catastrophizing

Pain catastrophizing was measured by the PCS Patient version (PCS-P) questionnaire. Comprising 13 items, the scale gauges three dimensions of pain catastrophizing: rumination (four items, e.g., “I keep thinking about how much it hurts”), magnification (three items, e.g., “I become afraid that the pain may get worse”), and helplessness (six items, e.g., “There is nothing I can do to reduce the intensity of the pain”). Respondents rank each statement on a 5-point Likert-type scale, ranging from 0 (*not at all*) to 4 (*always*), indicating the extent to which they experience these thoughts and feelings related to painful experiences. Scores are aggregated and can range from 0 to 52. The reliability (α =0.87) and validity of the scale has been widely endorsed in various studies (Osman et al., 1997; Sullivan et al., 2000). In this study, the Persian versions of PCS-P was employed, and its reliability (α =0.81) had been previously established in studies among Iranian populations (Mohammadi et al., 2012). It also demonstrated satisfactory reliability in the present study (α =0.82).

Depressive symptoms

To assess symptoms of depression, participants completed the Farsi version (Ghassemzadeh et al., 2005) of the Beck Depression Inventory (Beck et al., 1961). This questionnaire has 21 items, including apparent and reported sadness, inner tension, reduced sleep and appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Participants respond to the questions using a 4-point Likert-type scale from 0 (*not at all*) to 3 (*severely*), with higher aggregated scores indicating greater symptom severity. In a previous study, the translated Persian version of the BDI had acceptable reliability with a

Cronbach alpha of 0.82. In the present study, reliability was also acceptable (α = 0.80).

Fibromyalgia symptoms

The Persian (Mohammadi et al., 2012) adaptation of the revised Fibromyalgia Impact Questionnaire (FIQ) (Bennett et al., 2009) was used to ask 21 questions regarding participants' condition symptoms. Similar to the original FIQ, the Persian version is organized into three interconnected domains: (a) "function," encompassing 9 questions compared to the FIQ Persian version's 11, (b) "overall impact," featuring 2 questions that now specifically address the overall impact of fibromyalgia on functioning and symptom severity, consistent with the FIQ Persian version, and (c) "symptoms," including 10 questions versus 7 in the FIQ Persian version. Respondents use a zero to 10 Likert-type scale to indicate severity, with 10 being the worst. The function domain aggregate score (ranging from 0 to 90) is divided by 3, the overall impact domain score (ranging from 0 to 20) remains unchanged, and the symptoms domain score (ranging from 0 to 100) is divided by 2. The overall FIQ Persian version score is derived from the cumulative sum of these three adjusted domain scores. Prior research demonstrated the reliability of the scale (α = 0.88; Bennett et al., 2009), and it was also satisfactory in the present study (α = 0.82).

Statistical analysis

A series of mixed ANOVAs were used to analyze the data in IBM SPSSv25.0. The data were normal, with skewness and kurtosis scores within the +/- 2 acceptable range, and no outliers were detected. The demographic measures recorded in the study (age, height, weight, education, employment, time since diagnosis, physical activity baseline levels, and marital status) were compared across the three cohorts to ascertain if there were any significant differences between the groups before the intervention, as displayed in Table 1. The three groups did not significantly differ with respect to height, weight, marital status, time since diagnosis, physical activity levels, and employment status. However, there were differences for age and education.

Next, a series of mixed ANOVA 3 (groups) × 3 (time) were performed, where group was (1) AIR, (2) PA, and (3) control, and time was (1) baseline, (2) post-intervention (12 weeks), and (3) follow-up (8 weeks later). The Group x Time interaction effect was evaluated as well as time only and group only for each of the outcome variables: cognitive function, sleep disturbance, pain catastrophizing, depressive symptoms, and FM symptoms. For each variable, sphericity was violated. Therefore, the Greenhouse-Geisser correction was used, though the original degrees of freedom are reported with the relevant Greenhouse-Geisser epsilon value (ε).

The level of significance was set at $p \leq 0.05$, and partial eta squared (ηp2) effect sizes were reviewed for the mixed ANOVA results, with the following definitions. Small effect size: 0.01 ≥ηp2 ≥0.059, medium effect size: 0.06 ≥ηp2 ≥0.139, large effect size. ηp2 ≥0.14 ≥0.35, very large: ηp2 ≥0.36 ≥0.50, and extremely large: ηp2 ≥0.50. Cohen's *d* effect sizes were reported for pairwise comparisons, with 0.20 ≤d ≤0.49 indicating a small effect, 0.50 ≤d ≤0.79 a medium effect, 0.80 ≤d ≤1.49 a large effect, 1.50 ≤d ≤1.99 a very large effect, and d≥ 2.00 an extremely large effect. Small effect sizes are of negligible practical important, medium effect sizes of moderate practical importance, and

Table 1 Descriptive statistics and overview of sociodemographics

	Group			Statistics
Dimension	AIR	Physical activity	Control	
N	30	28	28	
Age (years): *M* (*SD*)	41.20 (10.87)	35.29 (8.65)	36.18 (7.72)	$F(2,83) = 3.49, p = 0.03$
Height (cm)	163.86 (5.76)	163.07 (5.26)	161.35 (5.10)	$F(2,83) = 1.62, p = 0.20$
Weight (Kg)	68.03 (9.20)	69.64 (10.40)	70.75 (11.89)	$F(2,83) = 0.49, p = 0.61$
Time since Fibromyalgia diagnosis (years): *M* (*SD*)	3.47 (0.76)	3.56 (1.0)	3.85 (1.0)	$F(2,83) = 0.63, p = 0.39$
Marital status (single/married): *n*	19/11	20/8	18/10	$c^2(N = 86, df = 8) = 0.49, p = 0.77$
Education (Diploma/Bachelor/Master/PhD): *n*	24/2/2/2	13/11/3/1	21/7/0/0	$c^2(N = 86, df = 8) = 16.79, p = 0.03$
Physical activity levels (not at all, very few, few, sometimes, much of time, very much: per week)	11/7/4/5/3/0	5/7/7/6/1/2	8/10/3/6/1/0	$c^2(N = 86, df = 10) = 10.52, p = 0.39$
Employment (unemployed, government-worker, self-employment)	22/6/2	20/4/4	18/5/5	$c^2(N = 86, df = 4) = 1.95, p = 0.74$

AIR, Amygdala insula retraining; *M,* mean; *SD,* standard deviation; *n,* number; *cm,* Centimeter; *Kg,* kilogram

$^*p < 0.05$. $^{**}p < 0.01$. $^{***}p < 0.001$

large, very large, and extremely large effect sizes are considered to of crucial practical importance.

Results

The mixed ANOVA analyses were conducted for each of the outcome variables, with the following results observed and displayed in Table 2.

Cognitive function Across the sample as a whole, the mixed ANOVA 3 (groups) × 3 (time) indicated that cognitive function increased from baseline to study completion and to follow-up for all three cohorts. As shown in Table 2, there were significant findings for Time x Group interaction (large effect size), time only (extremely large effect size), and group only (medium effect size). Bonferroni post hoc tests at post-intervention indicated there was a significant difference (p= 0.01) with a large effect size (Cohen's d= 1.27) between AIR and the control group, with AIR demonstrating a greater mean increase in cognitive function.

Table 2 Statistics for outcome variables by group and time

	Groups			Factors					
	AIR	Physical activity	Control	Group		Time		Time x Group interaction	
N	30	28	28						
	M (SD)	*M (SD)*	*M (SD)*	*F*	η_p^2	*F*	η_p^2	*F*	η_p^2
Cognitive Function				4.82* P=0.02	0.09	94.53* P=0.001	0.53	9.63* P=0.001	0.18
Baseline	58.83 (7.95)	60.53 (6.83)	60.17 (5.57)						
Post-intervention	69.63 (5.37)	68.17 (5.49)	63.28 (4.56)						
Follow-up	68.06 (5.79)	67.03 (6.42)	62.53 (4.81)						
Total Increase	9.23	6.50	2.36						
Percent Increase	15.69%	10.74%	3.92%						
Sleep disturbances				4.87* P=0.01	0.10	180.57* P=0.001	0.68	34.95* P=0.001	0.45
Baseline	11.30 (3.68)	9.78 (3.65)	9.85 (3.62)						
Post-intervention	4.46 (1.27)	6.89 (3.52)	8.67 (3.12)						
Follow-up	4.23 (1.07)	6.35 (3.09)	8.42 (3.51)						
Total Decrease	-7.07	-3.43	-1.43						
Percent Decrease	63%	35%	15%						
Pain catastrophizing				46.15* P=0.001	0.52	238.07** P=0.001	0.74	59.14* P=0.001	0.58
Baseline	41.90 (6.61)	43.17 (5.10)	43.10 (7)						
Post-intervention	21.13 (3.96)	35.03 (6.96)	40.17 (7.23)						
Follow-up	21.06 (4.61)	35.46 (6.70)	39.57 (6.52)						
Total Decrease	-20.84	-7.71	-3.53						
Percent Decrease	50%	18%	8%						
Depressive symptoms				13.69** P=0.001	0.24	250.20** P=0.001	0.75	27.29** P=0.001	0.39
Baseline	33.53 (7.11)	32.21 (7.57)	32.78 (5.93)						
Post-intervention	17.26 (2.62)	21.96 (6.39)	28.64 (6.50)						
Follow-up	17 (3.07)	21.71 (7.25)	27.85 (5.48)						
Total Decrease	-16.53	-10.50	-4.93						
Percent Decrease	49%	33%	15%						
FIQ scores				36.87* P=0.001	0.47	325.09** P=0.001	0.79	93.50* P=0.001	0.69
Baseline	60.50 (9.44)	59.25 (10.88)	60.96 (9.95)						
Post-intervention	28.56 (7.44)	49.82 (10.48)	55.71 (7.18)						
Follow-up	27.90 (8.40)	49.46 (10.42)	55.50 (9.31)						
Total Decrease	-32.60	-9.79	-5.46						
Percent Decrease	54%	17%	9%						

AIR, Amygdala and Insula Retraining; *PA*, Physical Activity; total increase/decrease = difference between baseline and follow-up; percent increase/decrease = percentage change between baseline and follow-up

Degrees of freedom: Group: (2, 83), Time: (2, 166), Time × Group (4, 166). *p <.05. **p <.01

Additionally, there was a significant difference (p= 0.02) with a large effect size (Cohen's d= 0.96) between PA and the control group, with the PA group experiencing a greater mean increase in cognitive function. AIR also yielded a greater mean increase than PA, though the difference only approached significance (p= 0.84) with small effect size (Cohen's d= 0.26). Still, AIR demonstrated the largest absolute increase in cognitive function across all groups, with a 15.69% improvement from baseline to follow-up compared to 10.74% increase in the PA group, and just a 3.92% increase in the control group. Figure 2 shows the marked difference in cognitive function for the AIR and PA groups compared to the control group.

Sleep disturbance The mixed ANOVA 3× 3 showed that in the sample as a whole, sleep disturbance decreased from baseline to intervention completion and to follow-up (see Table 2). There were significant results for Time x Group interaction (very large effect size), time only (extremely large effect size), and group only (medium effect size). The significant Time effect was primarily attributable to a reduction in sleep disturbance in the AIR and PA groups, whereas sleep disturbance scores remained nearly unchanged from baseline to follow-up in the control group. Pairwise comparisons showed a significant difference between AIR and the control group (p= 0.002) at post intervention, with a very large effect size (Cohen's d= 1.76) and AIR participants experiencing a greater mean reduction. However, the difference between PA and the control group only approached significance (p= 0.08), with a medium effect size (Cohen's d= 0.53). The AIR group showed a greater mean score reduction than the PA group, though it did not reach statistical significance (p= 0.17). However, the AIR group experienced the greatest absolute reduction in sleep disturbances, with a 63% decline from baseline to follow-up versus a 35% decline among the PA group, and a 15% decrease among the control group. The greater impact of AIR and PA on sleep disturbances as compared to the control group is displayed in Fig. 3.

Pain catastrophizing As highlighted in Table 2, the mixed ANOVA 3× 3 yielded that across the sample as a whole, pain catastrophizing decreased from baseline to post-intervention and to follow-up. There were significant results for Time x Group interaction, time only, and group only, all with extremely large effect sizes. There was a marked decrease in pain catastrophizing in the AIR and physical activity groups, whereas scores remained relatively

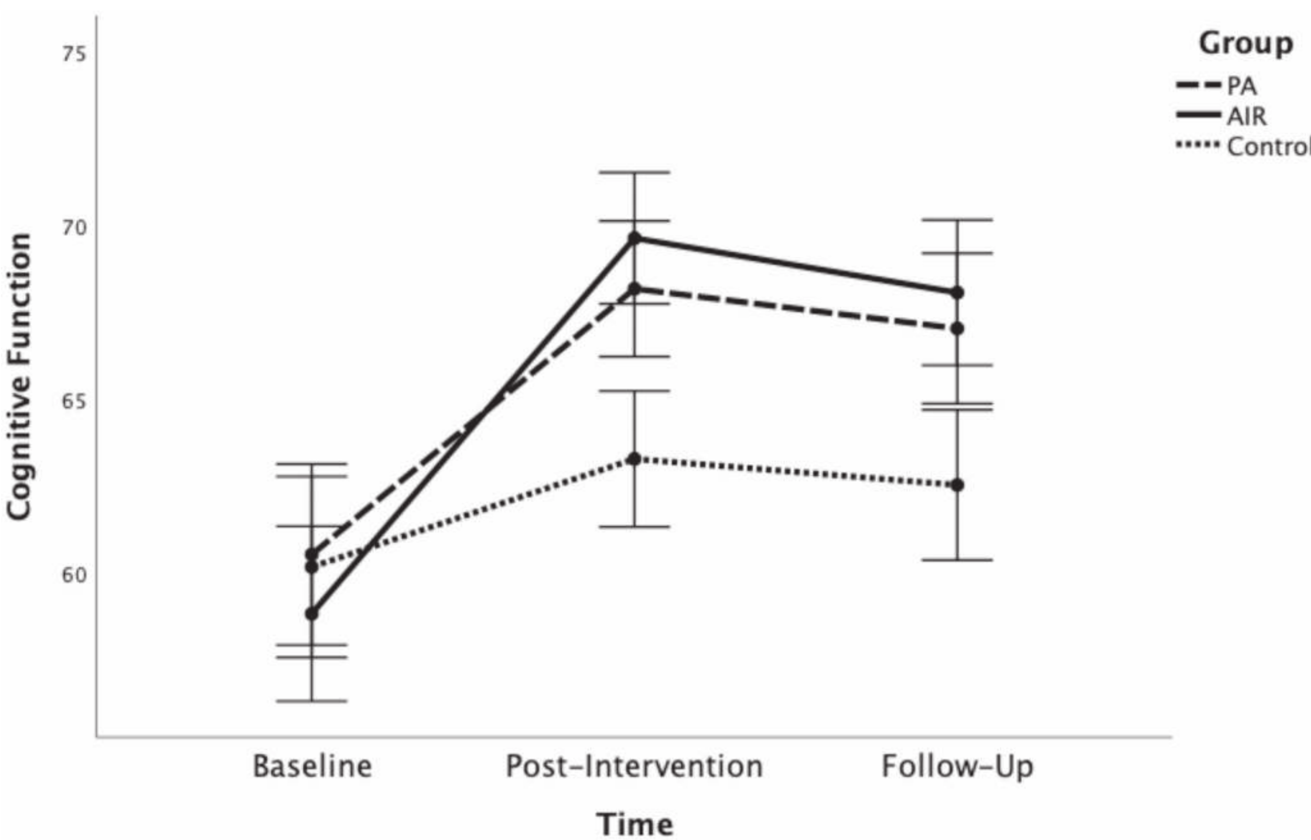

Fig. 2 Average levels of cognitive function for groups across the three study timepoints. *Note*: PA = physical activity; AIR = amygdala and insula retraining

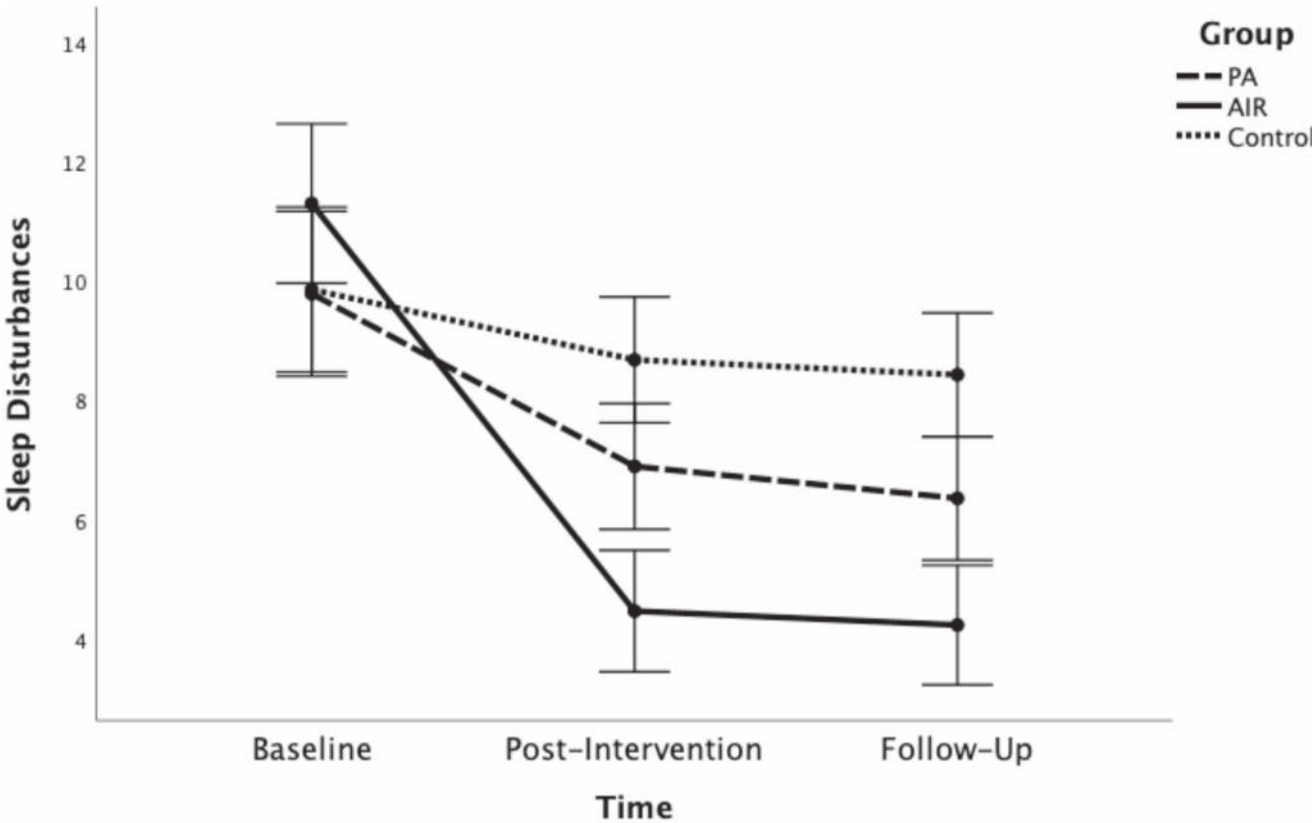

Fig. 3 Average levels of sleep disturbances for groups across the three study timepoints. *Note*: PA = physical activity; AIR = amygdala and insula retraining

unchanged in the control group. Indeed, AIR participants experienced a 50% decrease in pain catastrophizing from baseline to follow-up compared with 18% for the PA group and 8% for the control group. The pairwise comparisons also showed there was a significant difference between AIR and control group (p = 0.001), with an extremely large effect size (Cohen's d = 3.26). Moreover, there was a significant difference between physical activity and control group (p = 0.03), with a medium effect size (Cohen's d = 0.72). Finally, the AIR group experienced a greater reduction than the PA group that was statistically significant (p = 0.001), with an extremely large effect size (Cohen's d = 2.45). The superior performance of AIR in reducing pain catastrophizing is shown in Fig. 4.

Depressive symptoms Depressive symptoms decreased from baseline to post-intervention and to follow-up for all three groups (see Table 2). There were significant results for Time x Group interaction (very large effect size), time only (extremely large effect size), and group only (large effect size). Pairwise comparisons demonstrated a significant difference between AIR and control group (p = 0.001), with an extremely large effect size (Cohen's d = 2.29) and the AIR group experiencing a lower mean. There was also a significant difference between the PA and control groups (p = 0.002), with a large effect size (Cohen's d = 1.03) and the PA participants experiencing a lower mean. Moreover, between AIR and PA groups, AIR showed a lower mean, which was statistically significance (p = 0.05) with large effect size (Cohen's d = 0.96). The AIR group showed a 49% decrease in mean scores from baseline to follow-up, compared to a 33% decline in the PA group and a 15% reduction in the control group.

Fibromyalgia impact questionnaire (FIQ)

As shown in Table 2, the mixed ANOVA 3 (groups) × 3 (time) yielded significant findings for FIQ scores across Time x Group interaction effect (extremely large effect size), time only (extremely large effect size), and group only (very large effect size). Pairwise comparisons demonstrated a significant difference between AIR and control group (p = 0.001), with an extremely large effect size (Cohen's d = 3.71) and the AIR group experiencing a lower mean. Moreover, between AIR and PA groups, AIR showed a lower mean, which was statistically significance (p = 0.001) with large effect size (Cohen's d = 2.33). However, there was no significant difference between the PA and control

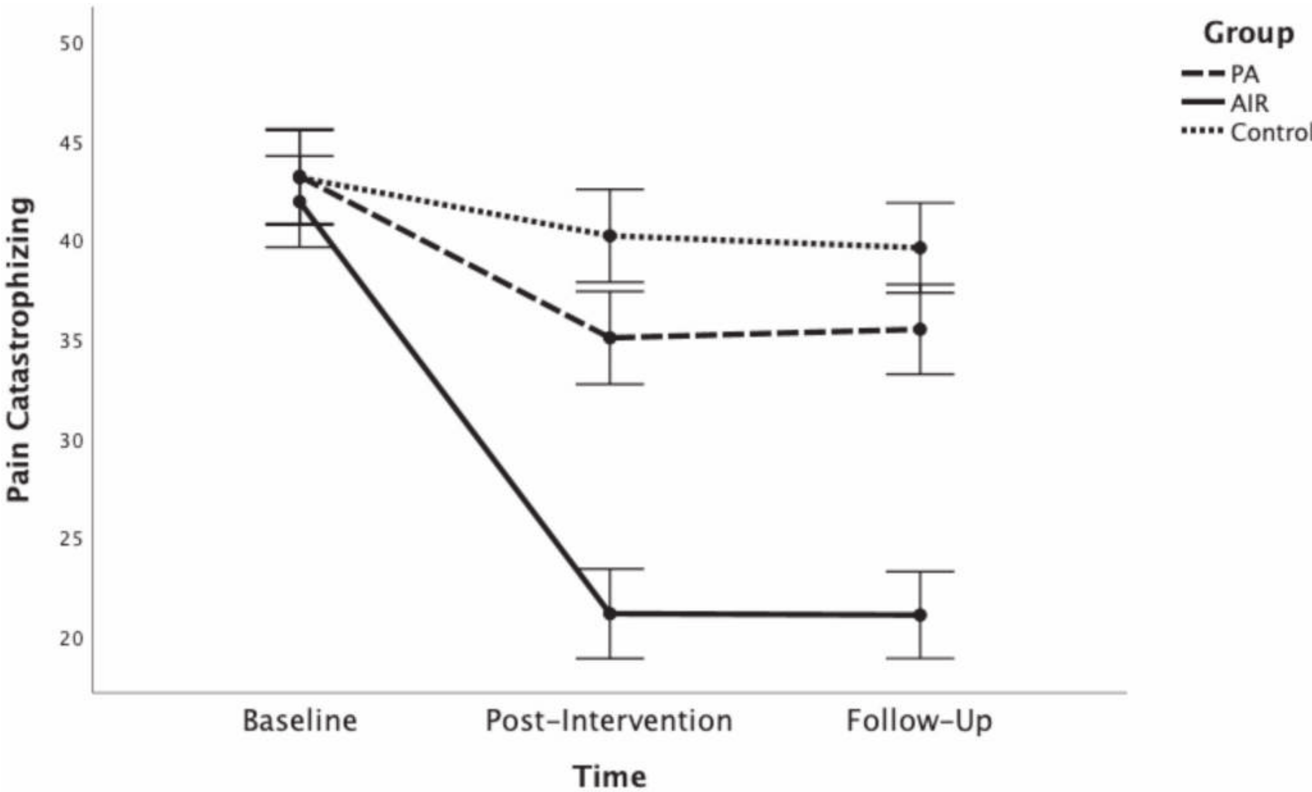

Fig. 4 Average levels of pain catastrophizing for groups across the three study timepoints. *Note*: PA = physical activity; AIR = amygdala and insula retraining

groups ($p = 0.14$). The AIR group showed a 54% decrease in mean scores from baseline to follow-up, compared to a 17% decline in the PA group and a 9% reduction in the control group.

Discussion

The present study examined the impact of two non-pharmacological interventions, AIR and PA, compared to medication as a control, on cognitive function, sleep disturbance, pain catastrophizing, depressive symptoms, and condition symptoms (FIQ) in women with FM. Results supported the hypotheses.

The first hypothesis posited that participants engaging in the AIR intervention would experience a significant improvement in cognitive function, sleep disturbances, catastrophic pain, depressive symptoms, and condition symptoms (FIQ scores). The second hypothesis suggested that participants engaging in a physical activity (PA) intervention would demonstrate a significant improvement in all outcome variables. The third hypothesis proposed that the two experimental groups (AIR and PA) would experience a significant improvement in outcome variables compared to an active control group receiving medication (Pregabalin). The study results indicated that both the AIR and PA interventions were effective in improving the various FM symptoms measured (H_1 and H_2) and that they were each more effective than the medication (H_3). Moreover, the AIR group demonstrated significantly better outcomes for pain catastrophizing, depressive symptoms, and FIQ scores compared to PA and the medication control group, and AIR consistently demonstrated the greatest increase (cognitive function) or decrease (all other measures) in mean scores from baseline to follow-up compared to the PA and control groups.

These results may be illuminated by the AIR intervention hypothesis. Namely, that the main cause of several chronic conditions, including FM, is maladaptive neuro-immune conditioning, rooted in the brain—specifically the amygdala and insula. Indeed, neuroscience research has suggested that the amygdala and insula along with other brain areas comprise a higher-order cortical network that control the brain's defense responses (LeDoux, 1998). More recent studies have demonstrated that the amygdala is primarily involved in monitoring for threats, sending out defense responses, and allocating meaning to neutral stimuli (Ehrlich et al., 2009). Consequently, the amygdala can perceive a non-threatening stimulus as threatening and assign it as such, thereby triggering an unnecessary defense response (Chudler & Dong, 1995; Ehrlich et al., 2009; LeDoux, 1998; Maren, 2001). This erroneous threat status is then stored in the insula, which is implicated in the acquisition and induction of defense responses (Pacheco-López et al., 2005). Thus, maladaptive defense responses can be activated when the amygdala and insula mistakenly interpret bodily symptoms, including pain signals, as threats (Gupta, 2002, 2010).

In practice, what this theory means is that an individual may experience a physical illness or acute traumatic event, but rather than the nervous and immune systems returning to a state of homeostasis after the illness or acute event has been handled, they get locked in a hypervigilant state because the amygdala and insula perceive the acute symptoms as a threat, which triggers defense responses that are unneeded and which manifest as further somatic symptoms, thereby creating a vicious cycle of danger signals being sent from the brain to the body and back again (Gupta, 2002, 2010). The AIR intervention is designed to interrupt this vicious cycle of danger signals and replace it with new, neural pathways that signal safety to the amygdala and insula. Thus, by targeting the hypothesized root cause of chronic illnesses like FM, the AIR intervention re-trains the amygdala and insula to help reduce the hyper-vigilance of the nervous and immune systems, including pain networks, and return the body back to normal (Gupta 2002, 2010).

Results from the present study are consistent with previous research that has demonstrated the effectiveness of AIR in addressing symptoms of FM (Sanabria-Mazo et al., 2020), ME/CFS (Toussaint et al., 2002), Long COVID (Toussaint & Bratty, 2023), and several other chronic conditions, such as mold illness, Lyme disease, and mast cell activation syndrome (MCAS; Bratty, 2024). Moreover, in some of these studies, the effectiveness of AIR significantly outpaced other therapies (e.g., treatment as usual, structurally equivalent wellness and relaxation programs) in improving the health status of participants. Our study supports Gupta's (2002, 2010, in publication) theory by demonstrating that AIR significantly improves fibromyalgia symptoms beyond what is typically achieved with standard medication alone (Sosa-Reina et al., 2017). By targeting the maladaptive neural pathways outlined in Gupta's theory, AIR offers a unique approach to modifying the brain's response to chronic pain and emotional distress (Bennett, 2019; Mobbs et al., 2015; Zhang et al., 2018). Physical activity further complements this by promoting neuroplastic changes, enhancing pain thresholds, and improving overall function (Hötting & Röder, 2013). The combined application of these interventions appears to address both the neurological and physiological dimensions of FM more comprehensively, offering a potential shift away from traditional pharmacological treatments. Future research should continue to explore these approaches, particularly focusing on how they can be optimized and integrated based on Gupta's theoretical framework to enhance patient outcomes in diverse populations.

While not quite as effective as AIR, the PA intervention also signficantly improved participants' symptoms for all the outcomes measures, and was more impactful than standard Pregabalin medication. Moreover, the impact of the current PA intervention aligns with previous research findings. A meta-analysis conducted in 2017, encompassing 14 randomized controlled trials (RCTs), highlighted the efficacy of PA in mitigating pain, enhancing overall well-being, alleviating symptoms of depression, and augmenting health-related quality of life across diverse FM patient cohorts (Sosa-Reina et al., 2017). The authors concluded that both aerobic and muscle strengthening exercises, consistent with the modalities employed in the present study, represent the most efficacious means of pain reduction and enhancement of overall well-being in individuals with FM. Furthermore, a recent meta-analysis involving 35 RCTs observed the effectiveness of various forms of exercise in ameliorating pain and depression among FM patients, with the exception of flexibility exercises (Kundakci et al., 2022). Furthermore, recent guidelines from the European League Against Rheumatism (EULAR) emphasized the prioritization of non-pharmacological interventions in FM management, notably highlighting exercise as the sole "strong" recommendation (Macfarlane et al., 2017).

The reason for the effectiveness of" PA' Improving FM outcomes may be due to the mechanisms underlying FM and the factors affecting symptom experience. Some studies suggest that exercise may have anti-inflammatory effects, which could be beneficial for FM patients as inflammation has been implicated in the pathophysiology of the condition (Masquelier & D'haeyere, 2021). Furthermore, PA has been shown to regulate neurotransmitters such as serotonin and dopamine, which play key roles in pain perception, mood regulation, and overall well-being. Dysregulation of these neurotransmitters has been implicated in FM, and exercise could help restore balance and alleviate the widespread pain associated with FM and improve mood (Norouzi et al., 2020; Sosa-Reina et al., 2017). PA may also help modulate central sensitization, a process implicated in FM where neural signaling within the central nervous system is amplified and leads to pain hypersensitivity (Katz et al., 2006; Norouzi et al., 2020). By desensitizing the nervous system through graded exposure to PA, patients may experience reduced pain sensitivity over time (Masquelier & D'haeyere, 2021; Sosa-Reina et al., 2017).

Engaging in PA may also serve as a distraction from pain, promote relaxation, reduce stress and may thereby, reduce pain perception (Norouzi et al., 2020; Pawlak et al., 2019). PA-induced improvements in mental health and mood could contribute to better coping mechanisms for managing FM symptoms (Norouzi et al., 2020; Sosa-Reina et al., 2017). Regular physical activity has been shown to improve sleep quality and duration (Khazaie et al., 2023). Since sleep disturbances are common in FM patients and can exacerbate symptoms, better sleep may contribute to overall improvement in functioning.

The present study's results are all the more striking considering that participants in the AIR and PA groups did not engage in those interventions along with treatment as usual. On the contrary, these particpants stopped taking their FM medications for the duration of the study and engaged only in AIR or PA for addressing their FM condition. This study design is arguably more stringent than the typical approach of allowing participants to continue their existing medication and treating the interventions as "add-ons."

From a practical perspective, the present study is noteworthy in demonstrating the positive impact of two non-pharmacological interventions in addressing various symptoms of FM. People with FM commonly suffer from cognitive dysfunction, sleep problems, pain catastrophizing, depressive symptoms, and various other condition-related issues. The observed improvements for all these variables in the AIR and PA groups underscore the potential of these interventions for improving the lives of FM patients, millions of whom struggle to manage their condition.

Strengths and limitations

The present study had two primary strengths. First, that it tested two non-pharmacological interventions against standard Pregabalin medication for treating FM. Second, that the study design was particularly stringent in that it required the two interventions to be the only source of therapy for FM for the duration of the study instead of the typical design of adding interventions such as these to treatment as usual. Still, several limitations should be acknowledged. First, the sample size was relatively small, potentially limiting statistical power. Second, the intervention duration of 12 weeks may not capture longer-term impacts or variations in responses over an extended period. Though an 8-week follow-up measure was included, future studies would benefit from more extended periods between the end of the intervention and a final set of measurements. Third, reliance on self-report measures introduces the possibility of response bias, as participants' subjective experiences with the interventions may affect the accuracy of the outcomes. Fourth, the lack of a control group in the intervention design raises challenges in attributing observed effects solely to the AIR and PA interventions. However, the experimental design with participants randomly allocated to groups helped to mitigate this shortcoming. Fifth, the study did not explore potential interactions between different intervention components (AIR and PA), leaving room for further investigation into their combined effects. Sixth, the online administration of the AIR program might impact the effectiveness of outcomes versus an in-person program. However, the study design incorporated weekly in-person gatherings of participants, which helped mitigate this potential concern. Seventh, the findings of this study contribute significantly to the existing literature on the psychological impact of AIR and PA in women with fibromyalgia. Future research endeavors should incorporate the evaluation of physical fitness parameters to gain a more comprehensive understanding of the multifaceted benefits these interventions offer to this population. Finally, it is worth noting that the focus of this study was to understand differences within and between groups. Future studies could expand understanding by exploring individual differences. These limitations underscore the need for a cautious interpretation of the results and suggest avenues for future research to address these constraints and enhance the robustness of findings in the field of FM management.

Practical implications

Though the present study had numerous limitations, it also offers several helpful practical implications. AIR and PA are promising interventions for patients, clinicians, and researchers seeking to address FM symptoms that are often varied and challenging to treat. Both interventions are low-cost and accessible. AIR is available via a member website and app, and PA exercises can be practiced with no equipment from home. Of course, clinicians and researchers should be mindful that the effectiveness of interventions might be influenced by the severity and range of FM symptoms, cultural variations in health beliefs, attitudes toward non-pharmacological interventions, and social support systems.

Conclusion

The present study provided valuable insights into the potential effectiveness of non-pharmacological interventions, Amygdala and Insula Retraining (AIR), and physical activity (PA) for alleviating cognitive dysfunction, sleep disturbances, pain catastrophizing, depressive symptoms, and condition symptoms among women with FM. The results indicated that both AIR and PA were significantly more effective than standard Pregabalin medication. Notably, the AIR intervention was most effective in improving all measured symptoms and was significantly superior in addressing pain catastrophizing (50% improvement from baseline compared to 18% for PA and 8% for medication), depressive symptoms (49% improvement compared to 33% for PA and 15% for medication), and overall FM impact (54% improvement versus 17% for PA and 9% for medication). While acknowledging the study's limitations, these findings are meaningful because interventions like AIR can potentially transform the landscape of FM management within healthcare systems, leading to a more patient-centric, cost-effective, and sustainable approach to treating FM patients. Future research with larger and more diverse samples, extended follow-up periods, and exploration of combining AIR and PA will further enhance our understanding of optimal strategies for comprehensive FM care. Overall, this study encourages a shift toward effective and practical non-pharmacological approaches in addressing the complex challenges posed by FM, aiming to improve the overall quality of life for individuals living with this condition.

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Authors' contribution E.N, H.K., M.P, A.B, T.A.J, P.S, S.A, participated in the design of the study, carried out the experiments and genotyping, analyzed the data, interpreted the results, and wrote the manuscript. E.N, H.K., A.B, contributed to the conception and design of the study, interpretation of data, and writing of the article. All authors read and approved the final manuscript.

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Data availability Data are available upon reasonable request.

Declarations

Consent for publication Not Applicable.

Ethics approval and consent to participate Informed consent was obtained from all participants and the Review Board of the Kermanshah University of Medical Sciences (Kermanshah, Iran) approved the study, which was conducted in accordance with the ethical principles in the Declaration of Helsinki and its later amendments (registration of a clinical trial: IRCT20210119050079 N2(.

Conflict of interests All authors declare no conflict of interests. Alexandra J. Bratty is the CEO of AB Research Consulting, which provides consulting services to The Gupta Program, the commercial version of the Amygdala and Insula Retraining (AIR) intervention. Her company was compensated for this work by independent donors.

References

Ambrose, K., Gracely, R., & Glass, J. (2012). Fibromyalgia dyscognition: Concepts and issues. *Reumatismo*, *64*(4), 206–215.

Arnold, L. M., Russell, I. J., Diri, E., Duan, W. R., Young Jr, J. P., Sharma, U., & Haig, G. (2008). A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. *The Journal of Pain*, *9*(9), 792–805.

Beck, A. T., Ward, C., Mendelson, M., Mock, J., & Erbaugh, J. (1961). Beck depression inventory (BDI). *Archives of General Psychiatry*, *4*(6), 561–571.

Bennett, K. (2019). Ancestral threats vs. modern threats. *TK Shackelford, & VA Weekes-Shackelford, Encyclopedia of Evolutionary Psychological Science*.

Bennett, R. M., Friend, R., Jones, K. D., Ward, R., Han, B. K., & Ross, R. L. (2009). The revised fibromyalgia impact questionnaire (FIQR): Validation and psychometric properties. *Arthritis Research & Therapy*, *11*(4), 1–14.

Bochenek, O., Koper, M., Nowak, A., Kałuża, J., Konaszczuk, A., Ratyna, K., & Skarbek, M. (2024). Beyond pills: Synergizing pharmacological and physical activity interventions in fibromyalgia treatment. A review. *Quality in Sport*, *19*, 53279–53279.

Bratty, A. J. (2024). Neuroplasticity intervention, amygdala and Insula retraining (AIR), significantly improves overall health and functioning across various chronic conditions. *Integr Med (Encinitas)*, *22*(6), 20–28.

Buysse, D. J., Reynolds, I. I. I., Monk, C. F., Hoch, T. H., Yeager, C. C., A. L., & Kupfer, D. J. (1991). Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh sleep quality index (PSQI). *Sleep*, *14*(4), 331–338.

Choy, E. H. (2015). The role of sleep in pain and fibromyalgia. *Nature Reviews Rheumatology*, *11*(9), 513–520.

Chudler, E. H., & Dong, W. K. (1995). The role of the basal ganglia in nociception and pain. *Pain*, *60*(1), 3–38.

Clauw, D. J. (2009). Fibromyalgia: An overview. *The American Journal of Medicine*, *122*(12), S3–S13.

Clauw, D. J. (2014). Fibromyalgia: A clinical review. *Jama*, *311*(15), 1547–1555.

Di Carlo, M., Bianchi, B., Salaffi, F., Pellegrino, G., Iannuccelli, C., Giorgi, V., & Sarzi-Puttini, P. (2024). Fibromyalgia: One year in review 2024. *Clinical and Experimental Rheumatology*.

Ehrlich, I., Humeau, Y., Grenier, F., Ciocchi, S., Herry, C., & Lüthi, A. (2009). Amygdala inhibitory circuits and the control of fear memory. *Neuron*, *62*(6), 757–771. https://doi.org/10.1016/j.neuron.2009.05.026

Farrahi Moghaddam, J., Nakhaee, N., Sheibani, V., Garrusi, B., & Amirkafi, A. (2012). Reliability and validity of the Persian version of the Pittsburgh sleep quality index (PSQI-P). *Sleep and Breathing*, *16*, 79–82.

Ghassemzadeh, H., Mojtabai, R., Karamghadiri, N., & Ebrahimkhani, N. (2005). Psychometric properties of a Persian-language version of the Beck depression Inventory-Second edition: BDI-II-PERSIAN. *Depression and Anxiety*, *21*(4), 185–192.

Häuser, W., Walitt, B., Fitzcharles, M. A., & Sommer, C. (2014). Review of pharmacological therapies in fibromyalgia syndrome. *Arthritis Research & Therapy*, *16*(1), 201. https://doi.org/10.1186/ar4441

Heidari, F., Afshari, M., & Moosazadeh, M. (2017). Prevalence of fibromyalgia in general population and patients, a systematic review and meta-analysis. *Rheumatology International*, *37*, 1527–1539.

Hong-Baik, I., Úbeda-D'Ocasar, E., Cimadevilla-Fernández-Pola, E., Jiménez-Díaz-Benito, V., & Hervás-Pérez, J. P. (2023). The effects of non-pharmacological interventions in fibromyalgia: A systematic review and metanalysis of predominants outcomes. *Biomedicines*, *11*(9), 2367.

Hötting, K., & Röder, B. (2013). Beneficial effects of physical exercise on neuroplasticity and cognition. *Neuroscience & Biobehavioral Reviews*, *37*(9), 2243–2257.

Jennings, E. M., Okine, B. N., Roche, M., & Finn, D. P. (2014). Stress-induced hyperalgesia. *Progress in Neurobiology*, *121*, 1–18.

Katz, R. S., Wolfe, F., & Michaud, K. (2006). Fibromyalgia diagnosis: A comparison of clinical, survey, and American college of rheumatology criteria. *Arthritis and Rheumatism*, *54*(1), 169–176. https://doi.org/10.1002/art.21533

Khaligh-Razavi, S. M., Habibi, S., Sadeghi, M., Marefat, H., Khanbagi, M., Nabavi, S. M., & Kalafatis, C. (2019). Integrated cognitive assessment: Speed and accuracy of visual processing as a reliable proxy to cognitive performance. *Scientific Reports*, *9*(1), 1102.

Khazaie, H., Norouzi, E., Rezaie, L., & Safari-Faramani, R. (2023). Effect of physical activity on sleep quality in patients with major depression disorder: A systematic review and meta-analysis of randomized controlled trials. *Current Psychology*, *42*(33), 28846–28856.

Kioussis, D., & Pachnis, V. (2009). Immune and nervous systems: More than just a superficial similarity? *Immunity*, *31*(5), 705–710.

Kizilbash, S. J., Ahrens, S. P., Bruce, B. K., Chelimsky, G., Driscoll, S. W., Harbeck-Weber, C., & Ninis, N. (2014). Adolescent fatigue, POTS, and recovery: A guide for clinicians. *Current Problems in Pediatric and Adolescent Health Care*, *44*(5), 108–133.

Kraus, A., Buckley, K. M., & Salinas, I. (2021). Sensing the world And its dangers: An evolutionary perspective in neuroimmunology. *Elife*, *10*, e66706.

Kundakci, B., Kaur, J., Goh, S. L., Hall, M., Doherty, M., Zhang, W., & Abhishek, A. (2022). Efficacy of nonpharmacological interventions for individual features of fibromyalgia: A systematic review and meta-analysis of randomised controlled trials. *Pain*, *163*(8), 1432–1445. https://doi.org/10.1097/j.pain.0000000000002500

LeDoux, J. E. (1998). *The emotional brain: The mysterious underpinnings of emotional life*. Simon and Schuster.

Macfarlane, G. J., Kronisch, C., Dean, L. E., Atzeni, F., Häuser, W., Fluß, E., & Jones, G. T. (2017). EULAR revised recommendations for the management of fibromyalgia. *Annals of the Rheumatic Diseases*, *76*(2), 318–328. https://doi.org/10.1136/annrheumdis-2016-209724

Maren, S. (2001). Neurobiology of Pavlovian fear conditioning. *Annual Review of Neuroscience*, *24*, 897–931. https://doi.org/10.1146/annurev.neuro.24.1.897

Marques, A. P., Santo, A. S. E., Berssaneti, A. A., Matsutani, L. A., & Yuan, S. L. K. (2017). Prevalence of fibromyalgia: Literature review update. *Revista Brasileira De Reumatologia*, *57*, 356–363.

Masquelier, E., & D'haeyere, J. (2021). Physical activity in the treatment of fibromyalgia. *Joint Bone Spine*, *88*(5), 105202.

Meulders, A. (2020). Fear in the context of pain: Lessons learned from 100 years of fear conditioning research. *Behaviour Research and Therapy*, *131*, 103635.

Mirzaei, A., Khaligh-Razavi, S. M., Ghodrati, M., Zabbah, S., & Ebrahimpour, R. (2013). Predicting the human reaction time based on natural image statistics in a rapid categorization task. *Vision Research*, *81*, 36–44.

Mobbs, D., Hagan, C. C., Dalgleish, T., Silston, B., & Prévost, C. (2015). The ecology of human fear: Survival optimization and the nervous system. *Frontiers in Neuroscience*, *9*, 121062.

Mohammadi, S., Dehghani, M., Sharpe, L., Heidari, M., Sedaghat, M., & Khatibi, A. (2012). Do main caregivers selectively attend to pain-related stimuli in the same way that patients do? *Pain*, *153*(1), 62–67.

Norouzi, E., Hosseini, F., Vaezmosavi, M., Gerber, M., Pühse, U., & Brand, S. (2020). Zumba dancing and aerobic exercise can improve working memory, motor function, and depressive symptoms in female patients with fibromyalgia. *European Journal of Sport Science*, *20*(7), 981–991. https://doi.org/10.1080/17461391.2019.1683610

Osman, A., Barrios, F. X., Kopper, B. A., Hauptmann, W., Jones, J., & O'Neill, E. (1997). Factor structure, reliability, and validity of the pain catastrophizing scale. *Journal of Behavioral Medicine*, *20*, 589–605.

Pacheco-López, G., Niemi, M. B., Kou, W., Härting, M., Fandrey, J., & Schedlowski, M. (2005). Neural substrates for behaviorally conditioned immunosuppression in the rat. *Journal of Neuroscience*, *25*(9), 2330–2337. https://doi.org/10.1523/jneurosci.4230-04.2005

Pawlak, M., Jazdzewska, A., & Leznicka, K. (2019). Can physical activity modulate pain perception during ontogenesis? *Baltic Journal of Health and Physical Activity*, *11*(3), 9.

Sanabria-Mazo, J. P., Montero-Marin, J., Feliu-Soler, A., Gasión, V., Navarro-Gil, M., Morillo-Sarto, H., & Luciano, J. V. J. J. O. C. M. (2020). Mindfulness-based program plus amygdala and insula retraining (MAIR) for the treatment O. women with fibromyalgia: A pilot randomized C.ntrolled trial. *Journal of Clinical Medicine*, *9*(10), 3246.

Sosa-Reina, M. D., Nunez-Nagy, S., Gallego-Izquierdo, T., Pecos-Martín, D., Monserrat, J., & Álvarez-Mon, M. (2017). Effectiveness of therapeutic exercise in fibromyalgia syndrome: A systematic review and meta-analysis of randomized clinical trials. *Biomed Research International*, *2017*, 2356346. https://doi.org/10.1155/2017/2356346

Steinman, L. (2004). Elaborate interactions between the immune and nervous systems. *Nature Immunology*, *5*(6), 575–581.

Sullivan, M. J., Tripp, D. A., & Santor, D. (2000). Gender differences in pain and pain behavior: The role of catastrophizing. *Cognitive Therapy and Research*, *24*, 121–134.

Thieme, K., Turk, D. C., & Flor, H. (2004). Comorbid depression and anxiety in fibromyalgia syndrome: Relationship to somatic and psychosocial variables. *Psychosomatic Medicine*, *66*(6), 837–844.

Toussaint, O., Royer, V., Salmon, M., & Remacle, J. (2002). Stress-induced premature senescence and tissue aging. *Biochemical Pharmacology*, *64*(5–6), 1007–1009.

Toussaint, L. L., & Bratty, A. J. (2023). Amygdala and insula retraining (AIR) significantly reduces fatigue and increases energy in people with long COVID. *Evidence-Based Complementary and Alternative Medicine*, *2023*(1), 7068326.

Vasheghani-Farahani, A., Tahmasbi, M., Asheri, H., Ashraf, H., Nedjat, S., & Kordi, R. J. A. J. O. S. M. (2011). The Persian, last 7-day. *Long Form of the International Physical Activity Questionnaire: Translation and Validation Study 2*(2), 106.

Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Katz, R. S., Mease, P., & Yunus, M. B. (2010). The American college of rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care and Research (Hoboken)*, *62*(5), 600–610. https://doi.org/10.1002/acr.20140

Wolfe, F., Walitt, B., Perrot, S., Rasker, J. J., & Häuser, W. (2018). Fibromyalgia diagnosis and biased assessment: Sex, prevalence and bias. *PLoS One*, 13(9), e0203755.

Zhang, X., Ge, T. T., Yin, G., Cui, R., Zhao, G., & Yang, W. (2018). Stress-induced functional alterations in amygdala: Implications for neuropsychiatric diseases. *Frontiers in Neuroscience*, *12*, 367.