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Compared to an active control condition, in persons with multiple sclerosis two different types of exercise training improved sleep and depression, but not fatigue, paresthesia, and intolerance of uncertainty

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ABSTRACT

Background: In persons with multiple sclerosis (MS), physical activity favorably impacts on psychological well-being. The aims of the present study were to investigate the influence of physical activity on depression, fatigue, sleep, paresthesia, and personality traits (intolerance of uncertainty), and to explore, if endurance training or coordinative training are superior to an active control condition.

Methods: 92 female individuals with MS (mean age: 37.36 years; mean EDSS: 2.43) took part in this intervention study. Participants were randomly assigned either to endurance training, coordinative training, or to an active control condition. At baseline, 4 weeks, and 8 weeks later at the end of the study, participants completed questionnaires on sleep, depression, fatigue, paresthesia and intolerance of uncertainty. Exercise training interventions took place three times/week for 45 min/session. Participants in the active control condition also met with the same duration and frequency.

Results: Sleep complaints and symptoms of depression decreased over time, but more so in the exercising groups, compared to the active control group. No changes over time and between groups were observed for fatigue, paresthesia, and intolerance of uncertainty.

Conclusions: Both endurance and coordinative exercising had the potential to favorably impact on some aspects of cognitive-emotional processing, while also an active control condition appeared to have a positive impact.

1. Introduction

Multiple sclerosis (MS) is a neurodegenerative disease (Reich et al., 2018; Thompson et al., 2018). For persons with MS (PwMS) impairments involve physical and psychological dimensions (Alghwiri et al., 2018) depression (Amtmann et al., 2015; Barzegar et al., 2018; Berzins et al., 2017; Boeschoten et al., 2017), sleep disturbances, fatigue, and paresthesia (Kallweit et al., 2018; Kallweit et al., 2013; Braley, 2018; Braley and Boudreau, 2016; Veauthier, 2015; Veauthier et al., 2013; Veauthier et al., 2016; Veauthier and Paul, 2014), along with a change (Sadeghi Bahmani et al., 2018) or decrease in physical activity levels (Latimer-Cheung et al., 2013; Motl et al., 2017; Pilutti et al., 2014; Platta et al., 2016; Motl et al., 2012; Veldhuijzen van Zanten et al., 2016) are typical complains of PwMS. There are different approaches to improve these dimensions, and given the tight interlinked characteristic between psychological and physical impairments, improvement in one dimension could be associated with improvements in other dimensions (Barzegar et al., 2018; Braley et al., 2016; Hughes et al., 2018; Induruwa et al., 2012; Sater et al., 2015).

The most common approach to treat symptoms of depression and sleep disturbances are pharmacological interventions, which mainly consists of antidepressants and benzodiazepines; due to their side effects, such medications are not proposed as a long-term treatment (Bamer et al., 2008, 2010; Thelen et al., 2014). Psychotherapy (mainly cognitive behavioral therapy (Clancy et al., 2015; Majendie et al.,

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2016)) and relaxation techniques (Dayapoglu and Tan, 2012; Fleming and Pollak, 2005; Kraft, 1998; Lisak, 2001) are other options. Besides, a growing body of research focuses on the impact of physical activity (PA) interventions on different symptoms of MS. These studies could show that physical activity programs are helpful interventions not only on fatigue and depression (Latimer-Cheung et al., 2013; Pilutti et al., 2014; Platta et al., 2016; Coote et al., 2017; Casey et al., 2018; Ensari et al., 2014b,a, 2015; Snook and Motl, 2009; Motl et al., 2009; Prakash et al., 2010; Razazian et al., 2016), but also on paresthesia (Razazian et al., 2016; Sadeghi Bahmani et al., 2019) and sleep (Sadeghi Bahmani et al., 2019; Siengsukon et al., 2016).

However, as regards the influence of regular PA on sleep patterns of PwMS, research is still scarce. This observation is astonishing: First, there is sufficient evidence from studies with both clinical and nonclinical samples that regular PA impacts favorably on subjective and objective sleep (Kalak et al., 2012; Brand et al., 2014; Lang et al., 2016; Mählmann et al., 2017; Kredlow et al., 2015; Chennaoui et al., 2015). Second, PwMS report more impaired sleep patterns, compared to healthy controls (Braley and Boudreau, 2016; Veauthier, 2015; Veauthier and Paul, 2014; Fleming and Pollak, 2005; Caminero and Bartolome, 2011). Third, only two studies showed some improvements of regular PA on sleep of PwMS (Sadeghi Bahmani et al., 2019; Siengsukon et al., 2016). Fourth, a major limitation of PA intervention studies with a control group was the set-up of the control condition: either they employed a passive control condition or a wait list making it thus difficult to estimate, if improvments were because of PA interventions or the social context. To counterbalance the methodological limitations observed in previous studies, in the present study, we introduced an active control condition to sort out possible effects in the PA condition due to the social context.

Next, we asked about the influence of a regular PA training on personality traits. Specifically, we investigated, if intolerance of uncertainty might improve after an eight-week-lasting PA-program. For the following reasons, this research question deserves more attention. First, in a previous longitudinal study we observed that among PwMS the personality trait of mental toughness did not change two years after disease onset (Sadeghi Bahmani et al., 2018). Second, the concept of intolerance of uncertainty is an important transdiagnostic variable within mood- and anxiety-related disorders which assesses the way an individual thinks and feels to be able (or unable) to cope with the insecurity of what will happen in the future. Not surprisingly, individuals with higher scores in intolerance of uncertainty interpret uncertainty more negatively. On the flip side, to explain the effectivness of regular PA on psychological dimensions, others (Knapen et al., 2005, 2015; Zamani Sani et al., 2016) emphazised on the increase of self-esteem, physical self-concept, stress-resistance, higher mood, higher interest in social interactions (Brand et al., 2018) and decreased rumination (Knapen et al., 2005; Knapen et al., 2015; Brand et al., 2018). Accordingly, it is also conceivable that after an intervention of regular PA intolerance of uncertainty might have decreased.

About two-thirds of PwMS report to experience fatigue (Branas et al., 2000). Fatigue is the sensation of physical and mental weakness and lassitude, which differs in the etiology and treatment from sleepiness (Popp et al., 2017): While the lack of sleep leads to sleepiness and could be treated with short naps or stimulants, the etiology of fatigue remains undisclosed; treatments consists of short rests (Popp et al., 2017) and physical activity: Reviews (Motl et al., 2017; Veldhuijzen van Zanten et al., 2016; Baird and Motl, 2019) and intervention studies (RA & SD) showed the favorable impact of regular physical activity on fatigue (Razazian et al., 2016; Sadeghi Bahmani et al., 2019). Accordingly, an aim of the present study was to further investigate, if and if so, to what extent regular physical activity might improve symptoms of fatigue.

Up to 87% of PwMS report paresthesia, that is, sensations of tingling, tickling, pricking, and burning (Minden et al., 2006). Contrary to fatigue, the influence of regular physical activity on paresthesia is much investigated, and to our knowldege, only two previous studies were able to show a favorable influence of physical activity on paresthesia.

Last, science and research are suffering from the so-called "Replication Crisis"; that is to say: Most findings reported in PubMed ® or other research search engines lack of replication, and fabrication and falsification of data is a serious scientific issue (Fanelli, 2009; Marusic et al., 2016; Wicherts, 2017). Specifically, Marusic et al. (2016) and Wicherts (2017) proposed to rigorously replicate previous results and to build up further research on the replicated and thus confirmed data. It follows that the replication of previous results is not a scientific flaw, but a necessity.

The following five hypotheses were formulated: First, following Sadeghi Bahmani et al. (2019), Kalak et al. (2012) and Lang et al. (2013) we expected that subjective sleep complains decreased in the exercise training conditions, compared to the active control condition (ACC). Second, following Razazian et al. (2016) and Sadeghi Bahmani et al. (2019) we expected that fatigue decreased in the exercise conditions, compared to the ACC. Third, likewise, we expected that symptoms of depression decreased in the exercise groups, compared to the ACC (Coote et al., 2017; Ensari et al., 2014; Razazian et al., 2016; Sadeghi Bahmani et al., 2019). Forth, following Razazian et al. (2016) and Sadeghi Bahmani et al. (2019) we expected a decrease in paresthesia score in the exercise conditions, compared to the ACC. Fifth, following Sadeghi Bahmani et al. (2018) we expected that intolerance of uncertainty as a proxy of personality did not change after an exercise intervention, and compared to an ACC.

We hold that the present study has the potential to add to the literature in an important way: First, we replicate previous findings; in doing so, we counteract the so-called replication crisis. Second, we expand upon previous findings in that we investigated the influence of exercise interventions in female PwMS in Iran, where such studies are still scarce. Third, we introduced an ACC to minimizing the risk that effects of exercise training condition might have been artificially biased due to the social context and social interaction. In so far, we hold, that the methodological framework of the study bares a crucial advantage, compared to studies conducted so far in the field.

2. Methods

2.1. Procedures

Female PwMS of the MS Society of Kermanshah province, located in the Farabi University-Hospital of the Kermanshah University of Medical Sciences (KUMS; Kermanshah, Iran) were approached to participate in the present intervention study. Eligible participants were fully informed about the aims of the study and the confidential nature of the data handling. Thereafter, participants signed the written informed consent. Next, participants were randomly assigned either to endurance training (ET), coordinative training (CT), or to an active control condition (ACC). At baseline, and four and eight weeks later at the end of study, participants completed questionnaires covering depression, fatigue, paresthesia, sleep complaints and intolerance of uncertainty (see below). Experts rated participants' degree of impairment with the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). Irrespective from the study conditions, sessions took place 3 times/week for about 45–60 min for eight consecutive weeks. The ethical committee of the Kermanshah University of Medical Sciences (KUMS; Kermanshah, Iran; IRCT 2016062423705N4;ww.irct.ir; KUMS.REC.1395.127), approved the study, which was performed in accordance with the ethical principles laid down in the seventh and current edition (2013) of the Declaration of Helsinki.

2.2. Participants

Female PwMS were consecutively enrolled in the study. Inclusion criteria were: 1. Age between 18 and 65 years; 2. Status of MS, as

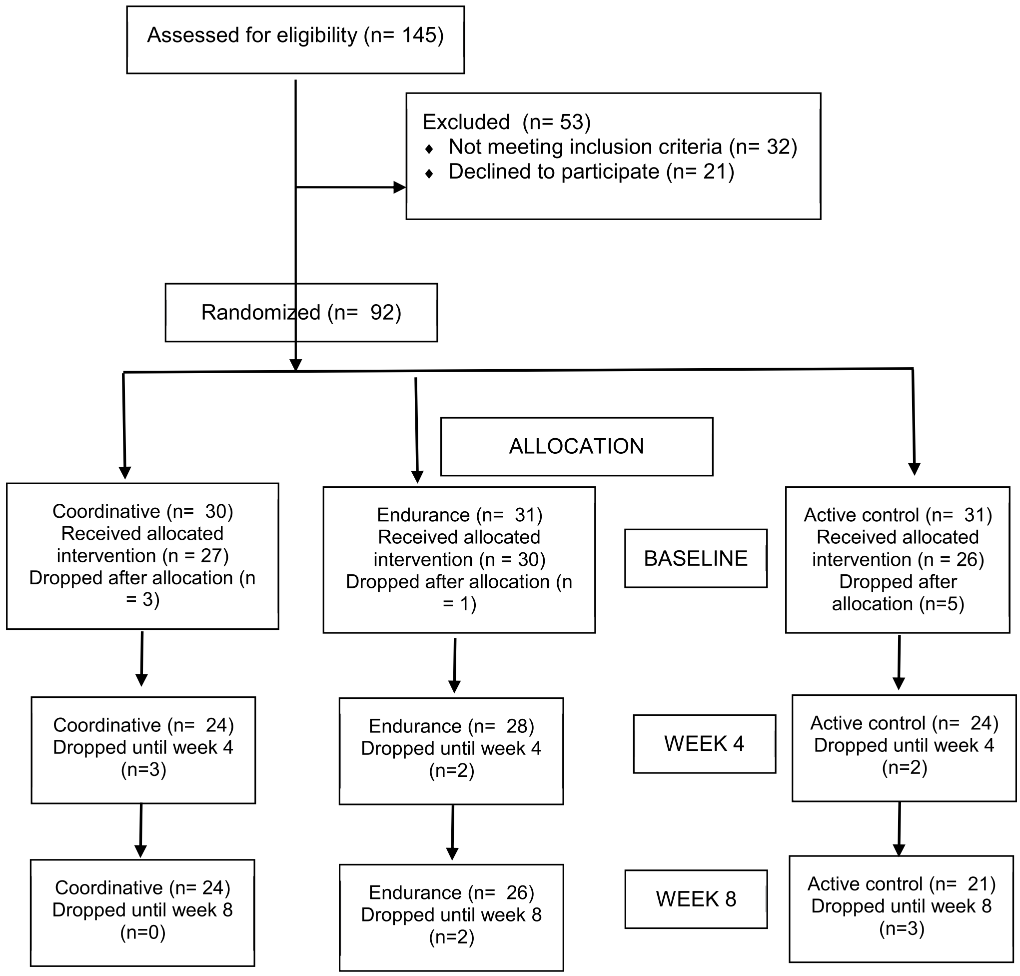

Fig. 1. Recruitment, eligibility, randomization, patients' group assignments, and number of patients per group at baseline, week 4 and week 8.

ascertained by a trained neurologist and based on Mc Donald's criteria; 3. EDSS score < 6; 4. Willing and able to comply with the study conditions; 5. Signed written informed consent. Exclusion criteria were: 1. Other neurological disease; 2. Severe psychiatric issues such as major depressive disorders, bipolar disorders, substance use disorder, anxiety disorders, post-traumatic stress disorders, attention-deficit-hyperactivity disorders, based on a thorough clinical psychiatric interview (Sheehan et al., 1998); 3. Acute suicidality; 4. Musculoskeletal issues which did not allow regular PA; 5. Participants missed more than 3 sessions; 6. The principle investigator excluded participants from the study, if a participant showed adverse events, which might have been associated with the interventions. 7. Undergoing further PA, psychotherapy, or undergoing surgery; 8. Pregnancy and/or breast feeding.

2.2.1. *Sample size calculation*

We performed a power analysis with G*Power (Faul et al., 2007) with the following statistical indices: Cohen's f for ANOVAs with repeated measures and within and between interactions: 0.16; alpha: 0.05; power (1-beta): 0.90; number of groups: 3, number of measurements: 3; calculated total sample size: 81. To counterbalance drop-outs, the sample size was set at $N = 93 = 31$ participants per group (see Fig. 1).

2.2.2. *Randomization*

Randomization occurred with the software randomization.com. Based on this list, a psychologist not otherwise involved in the study prepared 3 × 31 envelops with the specific study conditions. Envelops were sealed, with no further identification, put in an opaque and closed ballot box and stirred. Next, the responsible drew an envelope and assigned participants to one of the three study conditions. Once an envelope was drawn, it was put aside. Experts rating participants' EDSS scores were blind to participants' study condition assignments.

2.3. *Tools*

2.3.1. *Sociodemographic and MS-related information*

Participants reported on their age; MS-related information such as duration of MS and medication regimen were taken from medical records.

2.3.2. *Subjective sleep complaints*

Subjective sleep complaints were assessed with the Insomnia Severity Index (ISI; Bastien et al., 2001; Gerber et al., 2016)). This questionnaire is a seven-item screening measure for insomnia. The items, answered on a 5-point Likert scale ranging from 0 (=not at all) to 4 (=very much), refer in part to the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) criteria for insomnia by assessing difficulty falling asleep, difficulty remaining asleep, early morning awakenings, impaired daytime performance, low satisfaction with sleep, and worry about sleep. The higher the overall score, the more the participant is assumed to suffer from insomnia (Cronbach's alpha = 0.87).

2.3.3. *Depressive symptoms*

To assess symptoms of depression, we used the Beck Depression Inventory-Fast Screen (BDI-FS) (Benedict et al., 2003). The BDI-FS is a brief self-report inventory designed to evaluate depression in patients with medical illness. It consists of seven items, and every item has a set of four possible responses, representing different levels of symptom severity (e.g., sadness: 0 = "I don't feel sad"; 1 = "I feel sad"; 2 = "I'm sad all the time and I can't snap out of it". 3 = "I'm so sad/unhappy, that I can't stand it"). Higher scores reflect a greater severity of depressive symptoms (range:0–21) (Cronbach's alpha = 0.90).

2.3.4. Fatigue

To assess the level of fatigue, participants completed the Fatigue Severity Scale (FSS (Krupp et al., 1989)). The FSS consists of nine items, and answers are given on 7-point rating scales ranging from 1 (= not at all) to 7 (= definitively/almost always), with higher scores reflecting higher levels of fatigue. Cronbach's alpha = 0.91.

2.3.5. Paresthesia

Participants rated their degree of paresthesia on a 10-point visual analogue scale ranging from 0 (= no sensations at all) to 10 (= severe sensations).

2.3.6. Intolerance of uncertainty

The construct of intolerance of uncertainty (IU) was assessed with the 27-item Intolerance of Uncertainty Scale (Sexton and Dugas, 2009). Participants answered questions such as "Uncertainty makes life intolerable", or "When I am uncertain, I can't go forward" on 5-point rating scale (1 = not at all characteristic of me, 5 = entirely characteristic of me) indicating how much they agree with the item. The higher the overall score is, the more the respondent is assumed to be more intolerant of uncertainty (Cronbach's alpha = 0.93).

2.4. Interventions

2.4.1. Endurance training

Endurance training condition lasted for eight consecutive weeks and consisted of three weekly supervised and guided group sessions (30–45 min/each). After 5 min of warming-up and stretching, participants exercised for 25–35 min on treadmill, exercise bicycles or walking/jogging with individual pauses of 1–2 min, followed by 5 min of cooling down. At the end of a session, participants should have had the feeling to be slightly exhausted, but not severely exhausted. Professional instructors monitored the sessions and participants' level of performance and exhaustion. In this view, Meyer et al. (2016) showed that compared to a preferred exercise duration and intensity, keeping a prescribed exercise duration and intensity improved mood among individuals with major depressive disorders.

2.4.2. Coordinative training

Coordinative training lasted for eight consecutive weeks, and three supervised and guided group sessions the week for 30–45 min/session. After 5 min of warming up, exercises focused on CT such as balancing on a small bar, mirroring and imitating instructors' movements (such as dancing steps), balancing balls, mirroring participants' bouncing with the balls of different size, surface and weight, 'football-tennis', balancing with closed eyes on a rope on the floor and similar exercises. The CT required a higher level of object control and locomotor skills as well as interactions with other participants. Such exercise characteristics are suggested to increase coordinative demands and cognitive engagement (Best, 2010; Pesce, 2012).

At the end of a session, participants should have had the feeling to be slightly exhausted, but not severely exhausted. Professional instructors monitored the sessions and participants' level of performance and exhaustion. Cooling down lasted for about 5 min.

2.4.3. Active control condition (ACC)

For eight consecutive weeks, participants of the ACC met three times/week for 30–45 min/session at the hospital center to ensure that frequency, duration, and the degree social contacts of the control condition were identical to the endurance and resistance training conditions. The control condition was not a 'bona fide' condition, which would have been actually intended to elicit change in cognitive and emotional dysfunctional consequences (Goyal et al., 2014; Wampold et al., 1997; Jasbi et al., 2018). Most importantly, in the control condition, topics such as successful coping strategies were not treated and not proactively proposed by the clinical psychologist responsible to monitor the content of the control conditions. Rather, participants were encouraged to proposing and exchanging daily life experiences.

2.5. Statistical analysis

Data were analyzed per protocol. With a series of t-tests, and X^2-tests, data between study completers and study non-completers were compared. With a series of X^2-tests, sociodemographic data between the three groups were compared. Two calculate changes over time and between groups, a series of ANOVAs for repeated measures was performed with the factors Time (baseline, week 4, week 8), Group (ET, CT, ACC) and the Time by Group-interaction, and with depression, fatigue, paresthesia, sleep complains, and intolerance of uncertainty as dependent variables. Post-hoc analyses were performed following Bonferroni-Holms corrections for p-values. Associations between scores of EDSS, depression, fatigue, paresthesia and intolerance of uncertainty were calculated with a series of Pearson's correlations.

The nominal level of significance was set at alpha < 0. 05. Effect sizes were reported as partial eta squared (ηp^2), with $0.01 < \eta p^2 < 0.059$ indicating small [S], $0.06 < \eta p^2 < 0.139$ indicating medium [M], and $\eta p^2 > 0.14$ indicating large [L] effect sizes. Further, following Becker (1988), Cohen's d effect sizes were reported for the pre-post change within the three groups and between the three time points. Statistical analyses were performed with SPSS® 25.0 (IBM Corporation, Armonk NY, USA) for Apple Mac®.

3. Results

3.1. Completers and non-completers

Completers (n = 71) and non-completers (n = 21) did not differ as regards age, EDSS, depression, fatigue, paresthesia, sleep complains, and intolerance of uncertainty (all t's < 1.0, p's > .30).

3.2. Sociodemographic and MS-related information

At baseline, participants in the three groups did neither descriptively nor statistically differ as regards age, civil status, educational level, depression, fatigue, paresthesia, and intolerance of uncertainty (all F's and all X^2-tests < 1.00, p's > .50). For EDSS scores, there was a significant Group effect ($F(2, 70) = 3.62$, $p = .032$). The post-hoc analysis showed that compared to participants in the ACC, participants in the coordinative condition had higher EDSS scores (Table 1).

Tables 2, 3, 4a and b report all descriptive and inferential statistical indices; accordingly, statistical indices are not repeated in the text anymore.

3.2.1. Symptoms of depression

Symptoms of depression decreased over time, but more so in the exercise training groups (medium effect sizes), compared to the ACC (small effect sizes; see Table 3). Specifically, symptoms decreased from baseline to week 4 (medium effect sizes), while means did not change anymore from week 4 to week 8.

3.2.2. Sleep complaints

Sleep complaints decreased over time, but more so in the exercise training groups (medium effect sizes), compared to the ACC.

Table 1
Sociodemographic and clinical data of participants, separately for participants in the coordination, the workout and the active control condition.

Dimensions	Groups Coordination	Workout	Active control
N	24	26	21
	M (SD)	M (SD)	M (SD)
Age (years)	39.17 (8.66)	37.96 (8.69)	37.90 (9.91)
EDSS	3.38 (1.87)	2.46 (1.50)	2.02 (1.84)
Disease duration (years)	8.13 (6.37)	6.92 (6.81)	7.21 (6.57)
	n/n	n/n	n/n
Civil status (married/single)	12/12	20/6	15/6
Highest educational level (high school/higher education)	19/5	20/6	17/4

Notes: EDSS = Expanded Disability Status Scale.

3.2.3. Fatigue and paresthesia

Scores of fatigue and paresthesia did neither change over time, nor between and within groups (always small effect sizes).

3.2.4. Intolerance of uncertainty

Scores of intolerance of uncertainty did neither change over time, nor between and within groups (always small effect sizes).

4. Discussion

The key findings of the present study are that among a sample of female PwMS and compared to an ACC, two exercise training interventions (ET and CT) over eight weeks improved depression and subjective sleep. By contrast and against expectations, no advantages of exercise interventions were observed for fatigue and paresthesia. Additionally, in the line of previous studies, personality traits (here: intolerance of uncertainty) remained unchanged, always when compared to an ACC. The pattern of results adds to the current literature in an important way in that we showed that both ET and CT may have beneficial effects on some but not on all dimensions of psychological functioning in female PwMS.

Five hypotheses were formulated, and each of these is considered in turn.

With the first hypothesis, we expected that compared to an ACC both ET and CT improved subjective sleep complaints, and data did fully confirm this. Accordingly, the present findings replicated previous results both among PwMS (Sadeghi Bahmani et al., 2019; Siengsukon et al., 2016) and non-clinical samples (Kalak et al., 2012; Lang et al., 2013). However, the present results expand upon previous studies, in that such a pattern of result was observed in female PwMS with MS in Iran, where research in this field is still scare, and in that to our knowledge this is only the third study to investigating the influence of regular physical activity on sleep among PwMS.

With the second hypothesis we assumed that compared to an ACC two exercise interventions improved fatigue, though, data did not support this assumption. Accordingly, the present data are at odds with previous studies (Razazian et al., 2016; Sadeghi Bahmani et al., 2019). However, Rooney et al. (2019) mentioned in their review, that evidence on these associations is mixed, that is to say: Not all interventional studies were able to impact on fatigue in a significant fashion. From this point of view, the present data do rather support the notion that fatigue does not appear to be necessarily favorably influenced by physical activity interventions. The quality of the data does not allow a deeper understanding of the present pattern of results. While Rooney et al. (2019) argued that some studies were statistically underpowered, this was not the case in the present study (see power calculation). A reason might be that we compared the fatigue levels of the intervention studies with those of an ACC. However, a closer introspection shows that effect sizes of the fatigue levels within the intervention conditions did neither descriptively, nor statistically change over time and irrespective from the comparison with the ACC. Next, it is conceivable that the intensity of the interventions was such that participants might have felt tired, while misinterpreting feelings of tiredness with feelings of fatigue. While highly speculative, this interpretation would match with the notion that the perception and interpretation of bodily signals is a cognitive-emotional process of appraisal, which might also bear the risk of bias.

With the third hypothesis we expected that compared to an ACC, symptoms of depression increased over time in the exercising groups, and data did confirm this. The pattern of results is thus in accord with previous studies in the field of MS (Razazian et al., 2016; Sadeghi Bahmani et al., 2019) and in the field of major depressive disorders (Schuch et al., 2017, 2016a,b; Stubbs et al., 2018; Vancampfort et al., 2017).

With the fourth hypothesis we assumed that compared to an ACC paresthesia scores decreased in the physical activity groups, though data did not confirm this assumption. Accordingly, we were unable to confirm previous results (Razazian et al., 2016; Sadeghi Bahmani et al., 2019). While again the quality of the data does not allow a deeper understanding of the underlying mechanisms, we advance the following assumptions. As discussed for fatigue, it is possible that bodily sensations were misleadingly interpreted. In this view, as reported in Tables 2 and 3 and shown in Fig. 3, paresthesia scores increased in the ET group from baseline to week 4, which might suggest that exercising was perceived as strenuous. Similarly, the van Uthoff-effect (Giesser, 2015) describes the increase of body temperature following exercising in PwMS; it might be therefore possible that such an increase of body temperature might have been interpreted as uncomfortable and as an increased sense of paresthesia.

With the fifth and last hypothesis we assumed that scores of

Table 2
Descriptive overview of the depression, fatigue, paresthesia, intolerance of uncertainty, sleep complains, and EDSS scores, separately for assessment time (baseline, week 4 and week 8), and group (coordination vs. workout vs. active control).

	Assessment times Baseline			Week 4			Week 8/end		
	Coordination	Workout	Active control	Coordination	Workout	Active control	Coordination	Workout	Active control
N	24	26	21	24	26	21	24	26	21
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Depression	7.96 (6.67)	7.92 (5.11)	6.24 (4.47)	5.46 (4.95)	4.85 (3.65)	5.57 (3.65)	5.29 (5.75)	5.12 (4.65)	6.52 (4.91)
Fatigue	40.54 (13.99)	39.08 (12.64)	42.71 (13.34)	34.75 (13.44)	37.19 (14.25)	40.76 (13.32)	34.08 (15.15)	39.31 (17.23)	45.05 (11.77)
Paresthesia	4.75 (3.27)	4.77 (3.02)	4.67 (3.09)	3.88 (3.18)	5.50 (3.06)	4.29 (3.36)	3.63 (3.41)	4.85 (2.59)	4.05 (3.37)
Intolerance of uncertainty	79.58 (28.86)	81.27 (23.30)	78.29 (19.90)	–	–	–	76.04 (24.39)	76.77 (31.49)	75.10 (20.84)
Sleep complains	13.46 (5.81)	11.62 (5.23)	11.71 (5.43)	–	–	–	10.13 (4.92)	8.81 (5.41)	11.14 (5.39)
EDSS	3.38 (1.87)	2.46 (1.50)	2.02 (1.84)	–	–	–	3.10 (1.86)	2.27 (1.64)	1.98 (1.70)

Notes: EDSS = Expanded Disability Status Scale.

Table 3
Overview of the inferential statistics for the factors Time (baseline, week 4, week 8/end of study), Group (coordination vs. workout vs. active control), and the Time by Group-interaction.

	Time	Group	Time × Group interaction	Greenhouse-Geisser Epsilon
Degrees of freedom	(2, 136)	(2, 68)	(4, 136)	
	F $p\eta^2$ [EF]	F $p\eta^2$ [EF]	F $p\eta^2$ [EF]	
Depression	15.13*** 0.182 [L]	0.02 0.001 [T]	3.19* 0.086 [M]	.998
Fatigue	1.98 0.028 [S]	1.72 0.048 [S]	1.34 0.038 [S]	.980
Paresthesia	2.88 0.041 [S]	0.72 0.021 [S]	2.32 0.064 [M]	.987
Degrees of freedom	(1, 68)	(2, 68)	(2, 68)	
	F $p\eta^2$ [EF]	F $p\eta^2$ [EF]	F $p\eta^2$ [EF]	
Intolerance of uncertainty	1.45 0.021 [S]	0.07 0.002 [T]	0.02 0.000 [T]	1.00
Sleep complains	31.54*** 0.110 [M]	0.66 0.019 [S]	4.25* 0.320 [L]	1.00

Notes: EF = effect size; T = trivial effect size; S = small effect size, M = medium effect size; L = large effect size.
* $p < .05$.
*** $p < .001$.

Table 4a
Effect sizes for mean comparisons (depression, fatigue, paresthesia) from baseline to week 4, week 4 to week 8, and baseline to week 8 assessments, separately for the groups (workout and coordination, and active control groups).

	Effect sizes: Cohen's ds Depression			Effect sizes: Cohen's ds Fatigue			Effect sizes: Cohen's ds Paresthesia		
	Baseline-week 4 Cohen's d	Baseline - week 8 Cohen's d	Week 4- week 8 Cohen's d	Baseline-week 4 Cohen's d	Baseline - week 8 Cohen's d	Week 4- week 8 Cohen's d	Baseline-week 4 Cohen's d	Baseline - week 8 Cohen's d	Week 4- week 8 Cohen's d
Active control	0.16 (S)	0.06 (S)	0.22 (S)	0.15 (S)	0.19 (S)	0.34 (S)	0.12 (S)	0.19 (S)	0.07 (S)
Workout	0.69 (M)	0.57 (M)	0.06 (S)	0.14 (S)	0.02 (S)	0.01 (S)	0.24 (S)	0.03 (S)	0.23 (S)
Coordination	0.54 (M)	0.56 (M)	0.03 (S)	0.42 (S)	0.44 (S)	0.05 (S)	0.29 (S)	0.33 (S)	0.08 (S)

Notes: (S) = small effect size; (M) = medium effect size; (L) = large effect size.

Table 4b
Effect sizes for mean comparisons (sleep complaints, intolerance of uncertainty) from baseline to week 8 assessment, separately for the groups (workout and coordination, and active control groups).

	Effect sizes: Cohen's ds Sleep complaints Baseline-week 8 Cohen's d	Effect sizes: Cohen's ds Intolerance of uncertainty Baseline-week 8 Cohen's d
Active control	0.11 (S)	0.16 (S)
Workout	0.53 (M)	0.17 (S)
Coordination	0.62 (M)	0.13 (S)

intolerance of uncertainty would remain unchanged after the interventions, and data did confirm this assumption. Accordingly, we hold that the present data confirm the concept that physical activity interventions influence psychological states, but not psychological traits: By definition, psychological traits developed over time as the sum of problem-solving strategies to cope with conflicts and problems; accordingly, it seems rather unlikely that such consolidated traits might be modified by physical activity interventions. In a similar vein, Sadeghi Bahmani et al. (2018) showed that mental toughness scores, understood as personality traits, remained stable even two years after the diagnosis and the onset of MS. As a final consequence, we claim that physical activity interventions have the potential to modify state

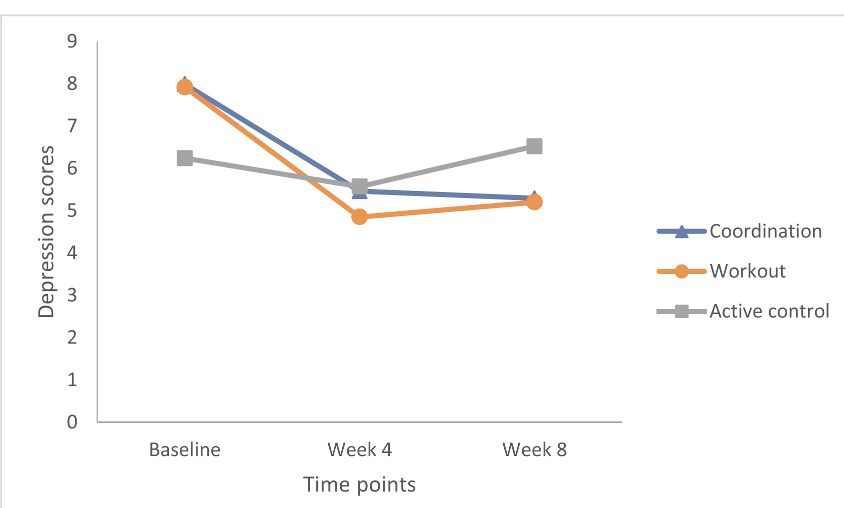

Fig. 2. Symptoms of depression decreased over time, but more so in the exercise training groups (medium effect sizes), compared to the active control condition (small effect sizes; see Table 3). Specifically, symptoms decreased from baseline to week 4 (medium effect sizes), while means did not change anymore from week 4 to week 8. Points are means.

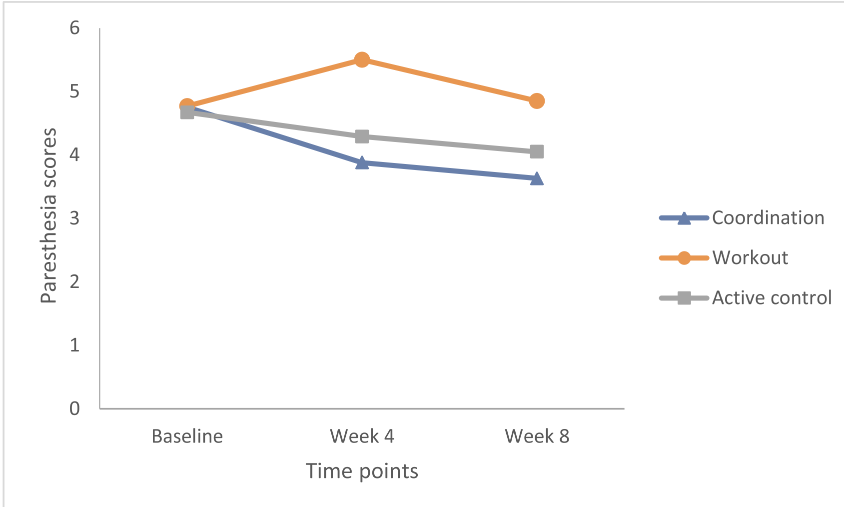

Fig. 3. Scores of paresthesia did neither change over time, nor between and within groups (always small effect sizes). Points are means.

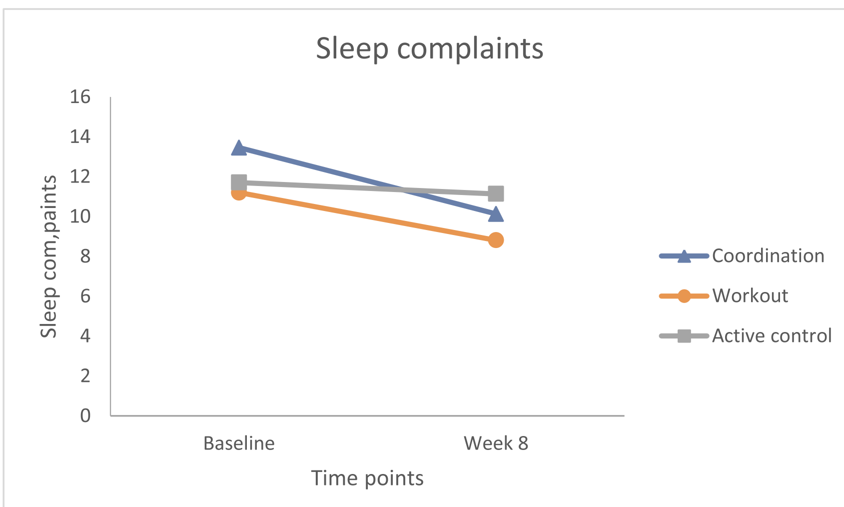

Fig. 4. Sleep complaints decreased over time, but more so in the exercise training groups (medium effect sizes), compared to the active control condition. Points are means.

variables, but not trait variables.

Despite the novelty of the data, several limitations warrant against the overgeneralization of the results. First, we assessed exclusively female patients with MS. For cultural and religious reasons, treatments and above all physical exercise interventions are gender-separated. Accordingly, it remains unclear, if and to what extend the present data are valid also for male individuals with MS, and accordingly, future studies (in Iran) should also pay more attention to male PwMS. Second, except for EDSS, we did fully rely on participants' subjective reports. However, further expert ratings such as depressive scores or anxiety scores or social interactional behavior (Brand et al., 2007) would have allowed to gain further insight in the impact of regular exercising on psychological functioning in PwMS. Likewise, third, it is conceivable that latent but unassessed psychological and physiological variables might have biased to or more dimensions in the same or opposite directions. Fourth, physical activity was not further assessed, while for instance actigraphs or apps on mobile phones to record one's physical activity behavior might have allowed to get more specific and objective pattern of activity. In this respect, actigraphs would have also allowed to assess objective sleep patterns. It follows that in future studies actigraphs should be employed to assess both objective physical activity and objective sleep patterns. Fifth, similarly, a simple Borg scale would have allowed to assess participants' level of exhaustion after the sessions. Sixth, participants' EDSS and psychological profiles showed that they were basically healthy; with "healthy" we understand that EDSS scores, but also sleep and anxiety and depression score were generally low to moderate. Accordingly, the chances to observe improvements did decrease, and not surprising, participants with higher EDSS showed higher improvements. Seventh, unlike other studies in the field, we applied an ACC, which in our understanding was able to sort out possible effects of exercise training due to social context and social interaction. Accordingly, it is conceivable that in previous studies using passive control group conditions, the beneficial effects on exercise training might have been in partly due to the social context. Eighth, a follow up assessment some weeks after study completion would have allowed to investigate, if and if so, the intervention had an impact at long term..

Declaration of Competing Interest

All authors declare no conflicts of interest. The entire study was performed without external funding.

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