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# Comparing the effect of aerobic exercises and guided imagery on depression in patients with multiple sclerosis

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## ABSTRACT

**Background:** Depression is commonly found in multiple sclerosis (MS), yet, it still undertreated. **Objective:** To compare the effect of aerobic exercise and Heal Light Guided Imagery (HLGI) on depression in patients with Relapsing-Remitting MS (RRMS) at short-term and one month follow up. **Methods:** A parallel group trial was conducted for eight successive weeks on 45 patients with RRMS, aged between 20 to 40 years old, and randomly assigned into three groups; 15 patients each. Aerobic exercise (AE) group received 30 minutes of stationary bicycle twice weekly, HLGI group received one session (60 minutes) weekly, and a wait-list control group. The Beck Depression Inventory (BDI), Fatigue Severity Scale (FSS) and Paced Auditory Serial Addition Test (PASAT), were measured pre-treatment, post-treatment and one month follow up. **Results:** The BDI showed significant reduction in AE and HLGI post-treatment and at follow up, with no statistical difference between the two groups. Compared with control group, the BDI was significantly reduced in intervention groups post-treatment and at follow up, while the FSS showed significant reduction in intervention groups only post-treatment. The PASAT showed significant increase post-treatment and at follow up in all groups, with no significant difference between them. **Conclusion:** Aerobic exercise and HLGI can similarly reduce depression in people with RRMS.

## KEYWORDS

Aerobic exercise; Healing light guided imagery; Depression; Multiple Sclerosis

## 1. INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune, inflammatory demyelinating disease of the central nervous system (CNS), and causes varying degrees of myelin destruction and axonal

degeneration of the CNS, which results in the loss of many functions of the body (Compston & Coles, 2008). Depression, fatigue, pain, and anxiety are considered as invisible symptoms in MS that result in greater health problems (White & Russell, 2008).

The prevalence of depression in patients with MS is predominant and sever, presented in about 50% of the patients. It is found in all types of MS, associated with worsening of disability and becomes more frequent with disease progression (Boeschoten et al., 2017; Solaro et al., 2018; Tarasiuk et al., 2022). The presence of depressive symptoms could also predict the onset of relapses in remitting-relapsing (RRMS) (Marrie et al., 2017; Rossi et al., 2017). Depression is frequently accompanied with fatigue in MS, and can negatively impact independence for daily living activities and quality of life (Marrie et al., 2012; Ploughman et al., 2020; Tarasiuk et al., 2022). Atrophy in the prefrontal cortex, the basal ganglia, the striatum, and the limbic system are commonly observed in patients with MS suffering from fatigue and depression (Heitmann et al., 2022).

Defining depression is usually stated in the literature to be difficult (Kamenov et al., 2014). The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines depressive disorder as a persistent depressed mood that causes significant distress and impairs psychological and social functioning. For being diagnosed with depression, the symptoms must be experienced nearly every day for at least two weeks. Depression includes combination of symptoms and characterized by the presence of five of nine symptoms; such as deep sadness, hopelessness, irritability, lack of interest or pleasure in previously enjoyed activities, changes in appetite with significant weight loss or gain, disturbed sleep; insomnia or hypersomnia, feelings of guilt, lethargy or worthlessness, fatigue, diminished concentration, disturbed memory, difficulty in decision making, symptoms like pain, cramps, headache, or digestive problems, and recurrent thoughts of death and suicide (National Institute of Mental Health, 2022; Torres, 2020; Jones et al., 2021).

Depression in MS could be related to primary or secondary causes. Primary depression is directly caused by the pathological changes of MS disease. Secondary depression is caused by the emotional stresses related to unpredictable course of disease, the social embarrassing of many symptoms of MS, side effect of some medications (e.g. corticosteroids, possibly interferon), sleep disorders, pain or coexistence of other diseases (Braley & Chervin, 2010; Pokryszko-Dragan et al., 2012). Treatment for MS-related depression commonly involves pharmacological (e.g. antidepressants), psychological (e.g. cognitive-behavior therapy (CBT), relaxation therapy), rehabilitation methods (e.g. exercise therapy), neuro-modulatory interventions (e.g. repetitive

transcranial magnetic stimulation, electroconvulsive therapy), yoga, and tai chi, and optimal diet. Antidepressant medication, CBT, and exercise therapy are the most common treatments of depression in MS (Bahji et al., 2019; Jones et al., 2021; Tarasiuk et al., 2022).

Aerobic exercise is simple and cost-wise training that protects against harmful consequences of stress (Salmon, 2001). Guided imagery (GI) is one of the relaxation therapies that uses mental images to influence the body physically and psychologically through the use of different senses (e.g. visually, auditory, sensory guided imaging) (Elgit et al., 2020). Healing Light guided imagery (HLGI) is reported to positively impact depression and fatigue in people with RRMS (Case et al., 2018). On reviewing literature, it is not clear which exercise therapies are superior to others, and whether a convinced exercise description is required to positively reduce depression in MS (Dalgas et al., 2015; Jones et al., 2021; Bilek et al., 2022). Up to authors knowledge, there is no study compared the effectiveness of aerobic exercises and HLGI on depression in MS. Therefore, the purpose of this study was to compare the effect of aerobic exercise and HLGI on depression in patients with RRMS at short-term and one month follow up.

## 2. METHODS

### 2.1. Study Design

Pre-test- post-test parallel study design was conducted from September 2018 to February 2019, and approved by the institutional review board at Faculty of Physical Therapy, Cairo University, Egypt (P.T.REC/012/001985), and followed the Guidelines of Declaration of Helsinki. Prior to study enrolment, each patient provided a signed informed consent after receiving full information about all study procedures.

### 2.2. Participants

Forty-five patients with RRMS from both sexes were recruited from the outpatient clinic at Faculty of Physical Therapy and Kaser Al-Ainy Multiple Sclerosis Unit (KAMSU), Cairo University, and randomly assigned into three equal groups. All participants were referred and diagnosed by a neurologist as clinically-defined RRMS according to the revised McDonald's criteria **(**Thompson et al., 2017**)**. To be include in the study, patients should meet the following criteria; clinically-defined RRMS who were medically stable at least during the previous three months, aged between 20 to 40 years old, with a disability level less than 4.5 on the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983**),** and having a score less than 15 on the Hospital Anxiety and Depression Scale (HADS) (Zigmond &

Snaith, 1983). Patients were excluded from the study if they have any of the following; other neurological deficits, orthopedic abnormalities, secondary musculoskeletal complications (e.g. contractures or deformities), cardiovascular, hepatic, renal, hemopoietic and thyroid diseases. Patients who received antidepressant medications (e.g. selective serotonin reuptake inhibitors (SSRIs), serotonin modulators, tricyclics and other norepinephrine-reuptake inhibitors), pregnant ladies or post-menopausal women, and illiterate subjects were all excluded. Subjects criteria were based on previous work (Ahmadi et al., 2013; Case et al., 2018; Solaro et al., 2018).

### 2.3. Randomization

A sample of forty-five patients were randomly assigned alternately (1:1:1) into the three equal groups; 15 patients each, by a blinded and an independent research assistant who opened sealed envelopes that contained a computer-generated randomization card.

### 2.4. Intervention

The used interventions were conducted by a qualified physiotherapist for eight successive weeks as following;

*The aerobic exercise group (AE, n=15)*

Patients in this group were treated by AE according to the Canadian physical activity guidelines for MS (Canning & Hicks, 2020). Thirty minutes of submaximal stationary endurance bicycle training (Stairmaster Spinnaker Bicycle ergometer. 3600. RC, made in Canada) was practiced with intensity of 65% to 75% of the age predicted maximum heart rate (MHR) which is the intensity preferable in patients with MS (Petajan et al., 1996). Patients were treated twice weekly for eight successive weeks. The session started by five minutes of warming up, followed by twenty minutes of training on the intended intensity, and terminated by five minutes of cooling down (Swank et al., 2013).

*The Healing Light Guided Imagery group (HLGI, n=15)*

Patients in this group were guided to relax through enhancing creative imagination using standardized visual cues. Patients were treated by a common sequence of standardized framework for 60 minutes once weekly. Individualized sequence was also practiced according to patient response to treatment. First, patient assumed a supine lying position to enhance relaxation. Breathing and induction process were also used to help patient to relax. Then, the patient was guided to imagine light entering the top of their head, and then saw a specific color or colors from the white light spectrum penetrating their mind and body, and providing relief (Menzies et al., 2014; Case et al., 2018). See appendix.

*The wait list-control group (n=15)*

Patients in this group did not receive any of the two interventions during the time of study conduction. As the study had been completed, patients were treated according to their evaluation, if they agreed to do (Case et al., 2018).

**2.5. Outcome Measures**

The study included three outcome measures. The primary measure included the Beck Depression Inventory (BDI), while the secondary measures included fatigue severity scale (FSS) and Paced Auditory Serial Addition Test with 3-second stimulus (PASAT#3). Measurements of all outcomes were conducted with a blind assessor at three-time intervals; baseline, post-treatment, and one month follow up.

*2.5.1. The primary outcome measures*

- *Beck Depression Inventory (BDI):* The BDI is a self-reporting questionnaire includes twenty-one items, valid and reliable in screening and measuring severity of depression symptoms in depressed and non-depressed psychiatric persons as well (Beck et al.,1961& 1988; Marrie et al., 2018). Each item of the BDI was ranked from zero to three**.** The sum score of all items represented the total score of the BDI with a minimum score of zero and maximum of 63. In depressed persons, a score between 0 to 9 indicates minimal depression, 10 to 18 indicates mild depression, 19 to 29 indicates moderate depression, and from 30 to 63 indicates severe depression (Beck et al., 1961& 1988**)**. An Arabic valid version of the questionnaire was used in the current work (West, 1985).

*2.5.2. The secondary outcome measures*

- *Fatigue Severity Scale (FSS):* Fatigue severity scale is a self-reported questionnaire consisting of nine statements that requires the subjects to rate their level of fatigue from one to seven. It is the most widely used method of evaluating fatigue in MS. Ratings was based on the experience of fatigue over the past seven days **(**Krupp et al., 1995). Valid and reliable Arabic version of the FSS scale for patients with MS was used in this study (Al-Sobayel et al., 2016).
- *The Paced Auditory Serial Addition Test* with 3-second stimulus *(PASAT#3):* The PASAT is considered a sensitive indicator of cognitive fatigability in MS; evaluating the cognitive function specially the auditory information processing speed and flexibility, as well as calculation (Walker et al., 2012). The PASAT can clearly identify impairment of divided attention, sustained attention, and working memory. During the test, random series of numbers from one to nine are presented and the subject consecutively add each number to the one that immediately preceded. The test was presented

on compact disc (CD) to control the rate of verbal stimulus every three seconds (PASAT#3). The tape is not stopped or paused during the task. The number of correct answers represented the PASAT#3 score, with a maximum of 60. PASAT has demonstrated good psychometric properties with high levels of internal consistency and test–retest reliability (Gronwall, 1977; Rosti et al., 2006; Tombaugh, 2006).

### 2.6. Sample size

According to previous studies (Ahmadi et al., 2013; Case et al., 2018), the number of participants required for final analysis was calculated to be 15 for each group considering the primary outcome of BDI. The OPEN-EPI program was used to calculate power analysis; a power of 0.80 with 95% confidence intervals (CIs) and α-level of 0.05.

### 2.7. Blinding

The study was a single-blind clinical study. Group allocation and assessment were blinded. The primary investigator and biostatistician were blinded to the treatment allocation.

### 2.8. Statistical methods

Data management and analysis were performed through the statistical package for social studies (SPSS) for windows, version 25. Prior to final analysis, data were screened for normality assumption, homogeneity of variance, and presence of extreme scores. The One-Way Analysis of Variance (ANOVA) was used to compare the general characteristics between the three groups. Values of the variables; BDI, FSS and PASAT#3 were all normally distributed, as assessed by Shapiro-Wilk's test ($p > 0.05$). There was homogeneity of variances, as assessed by Levene's ($p > 0.05$) for all variables. A linear relationship was found between the dependent variables as assessed by scatterplot, with no evidence of multicollinearity as assessed by Pearson correlation ($|r| < 0.9$). There were no univariate outliers in the data as assessed by inspection of a boxplot, and no multivariate outliers in the data as assessed by Mahalanobis distance. Mauchly's test of sphericity indicated that the assumption of sphericity was violated for the two-way interaction. Accordingly, 3x3 mixed MANOVA test was used to compare the tested variables of interest at three different measuring periods for the three groups. The level of significance for all statistical tests was set at $p < 0.05$.

## 3. RESULTS

A sample of eighty patients with RRMS were assessed for study eligibility. Forty-five subjects (19 males, 26 females) participated in the study and randomly assigned into three homogenous groups; 15 patients each. Figure (1) demonstrated the follow of participants throughout the study.

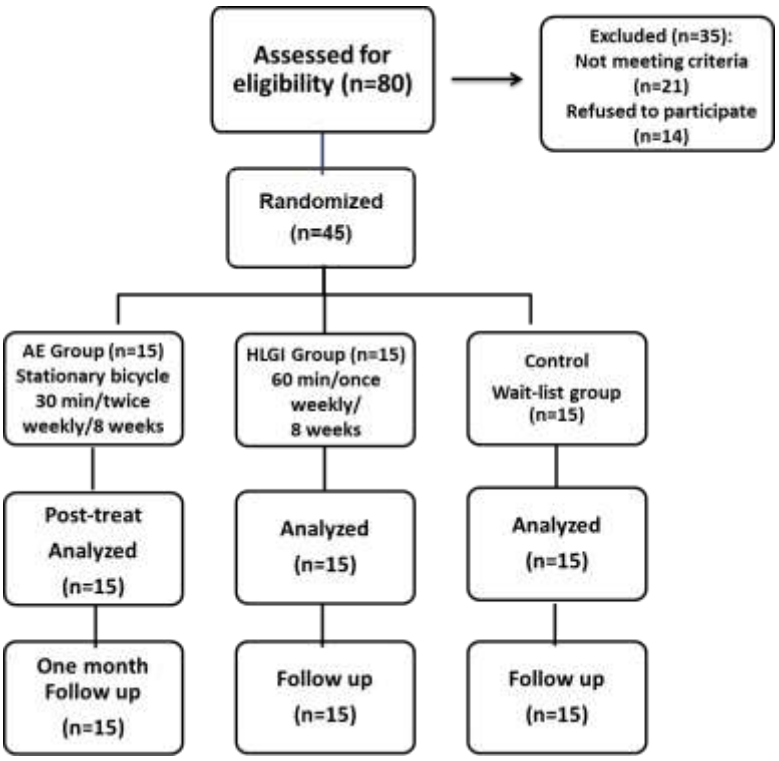


**Figure 1.** Participants flowchart throughout the study.

### 3.1. General Characteristics of Participants

There were no significant differences (P>0.05) between subjects in the three groups regarding their general characteristics (Table 1).

**Table 1.** General characteristics of participants in the three groups.

| | AE group | HLGI group | Control group | F-value | P-value |
|---|---|---|---|---|---|
| Age (years) | 30.93±6.58 | 28.6±5.39 | 30.2±4.79 | 0.671 | 0.517 |
| Height (cm) | 159.66±7.59 | 160.4±4.73 | 159±5.14 | 0.207 | 0.814 |
| Body mass (Kg) | 62.13±7.49 | 62.33±3.94 | 61.86±3.73 | 0.029 | 0.972 |
| BMI ($Kg/m^2$) | 24.27±1.66 | 24.17±.88 | 24.43±.92 | 0.173 | 0.842 |

*Values were expressed as (means±standard deviation). AE: Aerobic exercise. HLGI: Heal light guided imagery. *Significant value (p<0.05).*

### 3.2. Results of the 3×3 mixed design MANOVA

#### *3.2.1. The Overall effects*

The 3x3 mixed design MANOVA indicated that there were significant effects of the tested group on the BDI, FSS and PASAT#3 (F=2.35, P=0.038*). In addition, there were significant effects of the measuring periods (the second independent variable) on the BDI, FSS and PASAT#3 (F= 7.213, P=0.0001*). While, the interaction between the two independent variables (group and measuring

period) was no significant, which indicated that the effect of the tested group (first independent variable) on all the dependent variables was not influenced by the measuring periods (second independent variable) (F=1.297, P=0.239) (Table 2).

**Table 2.** The 3x3 mixed design MANOVA for all dependent variables at different measuring periods among groups.

| Source of Variation | F-value | P-value |
|---|---|---|
| Groups | 2.35 | 0.038* |
| Measuring periods | 7.213 | 0.0001* |
| Interaction | 1.297 | 0.239 |

**Significant value (p<0.05).*

### 3. 2 .2. Multiple pairwise comparison tests (Post hoc tests)

*3.2.2.1. Results of the BDI*

Within group comparison, the mean ± standard deviation (SD) values of BDI revealed a significant difference in AE and HLGI groups post-treatment and at follow up. Between groups comparison revealed no significant difference between AE and HLGI groups. A significant difference was detected between the intervention groups and control group in favor to intervention ones (Table 3).

**Table 3.** Descriptive statistics and 3×3 mixed design MANOVA of the BDI in the three groups.

| **The Mean± SD values of the BDI** | | | |
|---|---|---|---|
| | Pre-treatment | Post-treatment | Follow-up |
| AE | 20.2±6.38 | 15.6 ±5.28 | 15.8±6.69 |
| HLGI | 18.06 ±4.97 | 12.8±5.85 | 13.73±8.07 |
| Control | 21.6 ±6.2 | 22.8±8.02 | 22.4±8.06 |
| **Within group comparison for BDI (Post hoc tests)** | | | |
| | Pre-treatment vs. Post-treatment | Pre-treatment vs. follow up | Post-treatment vs. follow up |
| AE | 0.018* | 0.024* | 0.913 |
| HLGI | 0.007* | 0.026* | 0.612 |
| Control | 0.62 | 0.672 | 0.942 |
| **Between group comparison for BDI (Post hoc tests)** | | | |
| | AE vs. HLGI | AE vs. control | HLGI vs. control |
| Pre-treatment | 0.237 | 0.519 | 0.108 |
| Post-treatment | 0.245 | 0.006* | 0.0001* |
| Follow up | 0.463 | 0.023* | 0.003* |

*BDI: Beck Depression Inventory. AE: Aerobic exercise. HLGI: Heal light guided imagery. *Significant value (p<0.05).*

### *3.2.2.2. Results of the FSS*

Within group comparison, the mean ± SD values of FSS revealed a significant difference only in the AE group post-treatment. Between groups comparison, revealed a significant difference between each of the intervention group and control one in favor to intervention ones (Table 4).

**Table 4.** Descriptive statistics and 3×3 mixed design MANOVA of the FSS in the three groups.

| **The Mean± SD values of the FSS** | | | |
|---|---|---|---|
| | Pre-treatment | Post-treatment | Follow-up |
| AE | 4.79±1.02 | 3.97 ±0.91 | 4.44±1.34 |
| HLGI | 4.14 ±1.49 | 4.02±1.32 | 3.93±1.4 |
| Control | 4.98 ±1.27 | 5.04±1.13 | 4.99±1.04 |
| **Within group comparison for FSS (Post hoc tests)** | | | |
| | Pre-treatment vs. Post-treatment | Pre-treatment vs. follow up | Post-treatment vs. follow up |
| AE | 0.004* | 0.249 | 0.06 |
| HLGI | 0.671 | 0.489 | 0.705 |
| Control | 0.822 | 0.982 | 0.828 |
| **Between group comparison for FSS (Post hoc tests)** | | | |
| | AE vs. HLGI | AE vs. control | HLGI vs. control |
| Pre-treatment | 0.169 | 0.681 | 0.077 |
| Post-treatment | 0.898 | 0.013* | 0.018* |
| Follow up | 0.83 | 0.741 | 0.084 |

*FSS: Fatigue Severity Scale. AE: Aerobic exercise. HLGI: Heal light guided imagery. *Significant value (p<0.05).*

### *3.2.2.3. Results of the PASAT#3*

Within group comparison, the mean ± SD values of PASAT#3 revealed a significant difference in the three groups post-treatment and at follow up as well, with no significant difference between the groups (Table 5).

**Table 5.** Descriptive statistics and 3×3 mixed design MANOVA of the PASAT#3 in the three groups.

| **The Mean± SD values of the PASAT#3** | | | |
|---|---|---|---|
| | Pre-treatment | Post-treatment | Follow-up |
| AE | 42.33±11.37 | 48.13 ±8.53 | 50.13±5.99 |
| HLGI | 43.33 ±10.76 | 46.66±11.56 | 48.33±12.53 |
| Control | 40.8 ±8.22 | 46.86±10.03 | 47.53±9.53 |
| **Within group comparison for PASAT#3 (Post hoc tests)** | | | |
| | Pre-treatment vs. Post-treatment | Pre-treatment vs. follow up | Post-treatment vs. follow up |
| AE | 0.0001* | 0.0001* | 0.09 |
| HLGI | 0.035* | 0.014* | 0.156 |
| Control | 0.0001* | 0.001* | 0.566 |

| Between group comparison for PASAT#3 (Post hoc tests) | | | |
|---|---|---|---|
| | AE vs. HLGI | AE vs. control | HLGI vs. control |
| Pre-treatment | 0.79 | 0.683 | 0.501 |
| Post-treatment | 0.694 | 0.734 | 0.957 |
| Follow up | 0.615 | 0.468 | 0.823 |

*PASAT#3: The Paced Auditory Serial Addition Test with 3-second stimulus AE: Aerobic exercise group. HLGI: Heal light guided imagery. *Significant value ($p<0.05$).*

## 4. DISCUSSION

This study was designed to compare the effect of aerobic exercise and HLGI training on depression in patients with RRMS at short-term and one month follow up, contrasting to a control wait-list group. The symptoms of depression in the current work were improved in both AE and HLGI groups post-treatment and maintained at follow up, with no significant difference between the two groups. The groups of intervention were superior to control one at the short-term and follow up measures of depression symptoms. These obtained results revealed that receiving any of the intervention (AE or HLGI) can reduce the symptoms of depression in people with RRMS post-treatment, with a maintained effect after one month of treatment termination. This could clinically emphasize the use of any of the interventions to positively impact depression rather having no treatment.

The efficacy of guided imagery approach as a cognitive method is reported in managing patient pain and disability, and enhancing the sense of self-esteem (Menzies et al., 2014). The mechanism of action of HLGI is still not fully understood. However, practicing other GI modalities supported relaxation and significantly changed the activation of hypothalamic pituitary-adrenal axis (Lewandowski et al., 2013; Menzies et al., 2014). The individualized practice of the HLGI in this work instead of the generalized practice of other relaxation techniques could improve the depression in patients with MS. The repetition of positives thoughts and images during the practice of HLGI, is believed to create new pathways for the processing of patients thoughts, and therefore, improve his overcome the symptoms of depression and fatigue as well (Case et al., 2018). This information could explain the results of depression (BDI) and processing speed (PASAT) in the current work. The results of HLGI on depression in the current study came in agreement with the results of Case et al., 2018. The study of Beitollahi et al., 2022 reported positive effects of four weeks of auditory guided imagery on fatigue, stigma and mood of all types of MS.

The improvement of depression after AE in the present study can be explained by the reported antidepressant and anxiolytic effects of AE (Salmon, 2001, Ahmadi et al., 2013). The programmed exercises alter the neuro-endocrinologic mechanisms and also reduce the inflammatory cytokines. Aerobic exercise can stimulate both serotonin synthesis and serotonin receptor expression in patients with MS (Alvarenga-Filho et al., 2016), and consequently improve anxiety and depression. Additionally, physical activity is associated with increase of irisin serum level and brain-derived neurotrophic (BDNF) factor. Irisin modulates peripheral metabolism and increases the level of various anti-inflammatory proteins in the brain, and therefore enhances neural plasticity at supraspinal and cortical levels, and adapt to the central factors of fatigue as well (Zghal et al., 2015; Bilek et al., 2022).

The gradual progression of exercise intensity from low to moderate level according to patient tolerance could motivate the patients and improve their mood (Dalgas et al., 2015). Promoting neuroplasticity (Pedersen et al., 2019; Diechmann et al., 2021), improved cardiorespiratory fitness, (Dalgas et al., 2019), decreased sympathetic activity that improves sleeping (Al-Sharman et al., 2019), together with improved muscle strength, activity tolerance, mobility, walking capacity and quality of life (Solaro et al., 2018), can all play a role in improving depressive symptoms and fatigue perception in people with MS.

The results of AE on depression in this work were consistent with other studies (Ahmadi et al., 2013; Briken et al., 2014; Bilek et al., 2022). The study of Swank et al., 2013 also reported positive impact of eight weeks of AE on depression in MS, that was maintained at three months follow up. In contrast, other studies reported non-significant effect of AE on depression in MS (Learmonth et al., 2012; Oken et al., 2004; Schulz et al., 2004). The contrasting results could be related to the differences in subjects' disability level (EDSS 5 to 6.5 in Learmonth et al., 2012, while in our study the EDSS was less than 4.5), type of MS (all types were included in Schulz et al., 2004 while work only included RRMS), outcome measures (using HADS in Schulz et al., 2004 while BDI was measured in this study), treatment duration (40 minutes in Learmonth et al., 2012) or frequency (once weekly in Oken et al., 2004).

In the concern of fatigue, a significant improvement was only detected in AE group post-treatment, however, no change was detected in HLGI group These results could be explained by the effects of AE on fatigue-related MS at both peripheral (Motl et al., 2012) and central (Fimland et al., 2010) levels. During AE, the work of large muscles helps in improving muscle strength, endurance, mobility, cardiopulmonary functions (Solaro et al., 2018; Dalgas et al., 2019) and enhances the neuroplasticity at central level (Pedersen et al., 2019; Diechmann et al., 2021; Bilek et al., 2022,).

However, the HLGI mainly involves mental work through the guidance of creative imagination with no physical activity.

Compared with control group, the AE and HLGI groups in this work showed remarkable results of fatigue perception post-treatment. The results of follow up revealed non-significant differences between the three groups. Clinically, these results indicated that AE and HLGI would be beneficial for fatigue perception in RRMS rather than no treatment at short-term, while the maintenance of AE effect can not be guaranteed. In 2014, Schmidt and Wonneberger reported that AE had a significant, but weak effect on fatigue-related MS, which could explain the non-maintained effect at follow up in this work. Additionally, fatigue is a subjective multifactorial symptom and can be influenced by many factors (Flachenecker et al., 2002), thereby, there is no guarantee to maintain the obtained results of fatigue.

The positive impact of AE on fatigue perception in this work were consistent with the results of Bilek et al., 2022, Alvarenga-Filho et al., 2016, and Ahmadi et al., 2013 and contrary to other studies (e.g. Heine et al., 2017, Surakka et al., 2004). The contrasting results could be related to different disability level (higher EDSS in Heine et al., 2017), different outcome measure (Ambulatory Fatigue Index in the Surakka et al., 2004) and finally the subjectivity and multidimensionality of fatigue that could alter fatigue perception among patients (Flachenecker et al., 2002).

In the concern of central processing speed (PASAT), the present study showed a significant improvement post-treatment in all of the three groups, with no statistical difference between them. The improvement was maintained at follow up compared to the pre-test measurements in all of the three groups. PASAT is an important component of the MS functional composite, and is the most preferable cognitive and neuropsychiatric tests for MS (Fischer et al., 1999; Cortés-Martínez et al., 2019). These obtained results could be explained by the acceptable PASAT scores for our participants at baseline (the mean values of PASAT#3 were as following; AE; 42.33±11.37, HLGI; 43.33 ±10.76, and control; 40.8 ±8.22), as the normal scores of PASAT#3 was about (50.4) for subjects more than 12 years of education (Tombaugh, 2006). In addition, The PASAT is administered as a cognitive test that is similar to a game. Patient motivation and encouragement, and the creation of suitable and helpful environment during the test administration can all help to lessen the stressful nature of the test, and so eliminate the possibility of false-positive PASAT ratings (Sandry et al., 2016, Rosti et al., 2006).

In this work, the significant improvement of PASAT after AE agreed with that of Bilk et al., 2022. Recent review studies reported that AE and other physical activity can induce cognitive changes. Muscle activity increases the serum irisin which leads to an increased BDNF production in the CNS

and brain. The BDNF is related to the neural plasticity and improved hippocampal function, learning and memory (Pedersen et al., 2019; Diechmann et al., 2021). In contrast, other review studies revealed non-significant effect of exercise on cognitive performance in MS that was explained by the variability in subjects' criteria and exercise description; intensity, frequency and duration (Gharakhanlou et al., 2021; Kara et al., 2017). This study had some limitations. First, the uncontrollable psychological and emotional status of patients could influence the results. Second, patient compliance to treatment could be a limitation. Finally, the effect of each intervention on the neural plasticity, biomarkers, cardiopulmonary and neuro-motor systems were not evaluated in this study, and could be recommended for future work to provide further explanation and deep analysis of results.

## 5. CONCLUSION

Aerobic exercise and HLGI showed similar impact on depression in RRMS. Any of the interventions can be recommended for eight weeks in patients with RRMS as simple, safe and cost-wise method to improve depression at short-term with maintained effect at one month of follow up. Any of the interventions could significantly reduce fatigue perception compared to control group, but the results cannot be maintained. Future studies can be recommended to investigate the effect of AE and HLGI on depressive symptoms in different types of MS and variable sample characteristics at short-term and one month follow up. Neurophysiological changes could be also studied for deeper understanding of HLGI mechanism of working.

## APPENDIX

### Components of the HLGI practice (Case et al, 2018)

The following was a standardized HLGI session, which was individualized depending on the patient needs and his response to treatment. Patient assumed a supine lying position.

1. The session started by breathing exercise and an induction process to relax the patient.

2. When relaxed, the patient was guided to imagine that he walked over a set of twenty stairs. Once arrived the top of stairs, the patient was asked what he is aware of.

3. Depending on how they visualize the stairs, the patient and therapist either descend the stairs together (to enhance patient learning and experience.

4. Then, patient imagined a favorite chair that they would feel comfortable sitting in.

5. The next step is to imagine seeing a rainbow and a specific color will be obvious.

Depending on his creative imagination, the patient either saw or did not see the rainbow. If the patient only saw only a single-color light (usually white), many steps and preparations were made until their creative imagination allow visualization of additional colors of the rainbow.

6. Then, the patient was asked to imagine that he can hold this light in their creative imagination for their precise needs at that moment- for example, imagining the light was passing through neural pathways, and supporting the nervous system. The patient frequently describes this as tingling. Once the patient has the ability to work with that light, the same support process was done for other body organs and systems; and that the patient saw his systems lighting up. During practice, minimal changes in the patient's posture and expression and additional suggestions might be provided to allow them deeply engaged in this process.

7. At the end of the session, the patient was gradually taken out of the guided imagery state. The patient and therapist ascended the stairs together.

8. The session terminated with a conclusion and discussion of the patient's experience, and what to do at the upcoming week.

## 5. REFERENCES


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The authors declare no conflict of interest.

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