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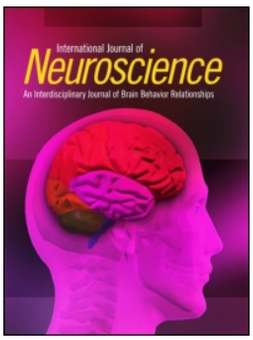

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Therapeutic effects of aerobic exercise on EEG parameters and higher cognitive functions in mild cognitive impairment patients

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Abstract:

Background: Mild cognitive impairment (MCI) is becoming an emerging problem for developing countries where there is an increase in expected age. There is no specific curative therapeutic treatment available for these patients.

Objective: The objective of this study was to evaluate short and long-term changes in the electroencephalogram (EEG) parameters and cognition of MCI patients with aerobic exercises.

Methods: A randomized controlled trial was conducted on 40 patients which were randomly divided into two groups, "aerobic exercise treatment group (n=21)" and "no-aerobic control group (n=19)". Short-term effects of exercise were measured after single session of exercise and long-term effects were measured after an 18 sessions (6 weeks) treatment. The outcomes which were measured were, electroenphelogram paramaters (slowness and complexity of the EEG) and cognitive functions (using mini-mental state examination (MMSE), Montreal cognitive assessment (MoCA), and trail making test (TMT) A and B).

Results: After one session of aerobic exercise there were significant improvements in slowness (delta waves; 0.678$\pm$0.035 vs 0.791$\pm$0.033; p=0.015) and complexity (0.601$\pm$0.051 vs 0.470$\pm$0.042; p=0.027) of the EEG in aerobic exercise treated group as compared to no-aerobic exercise group. After six weeks there were significant improvements in slowness (delta waves; 0.581$\pm$0.036 vs 0.815$\pm$0.025; p=0.005) and complexity (0.751$\pm$0.045 vs 0.533$\pm$0.046; p=0.001) of the EEG in the aerobic group as compared to no-aerobic group. Moreover, significant improvements were observed in the MMSE (p=0.032), MoCA (p=0.036), TMT-A (p=0.005) and TMT-B (p=0.007) in aerobic exercise group as compared to no-aerobic group.

Conclusion: Aerobic exercise showed improvement in cognition after short and long-term treatment in MCI subjects and can be used as potential therapeutic candidate.

Key words: Aerobics exercise; Emotiv; MCI; memory; slowness and complexity of EEG.

Introduction

Mild cognitive impairment (MCI) is the most rapidly developing problem and affects the elderly population [1]. It is a clinical condition in which people are found to a have minor deficit in cognitive functions and they also exhibit poor motor control [2]. MCI is a risk factor for developing Alzheimer's disease and/or dementia [1]. Pakistan is the 6th most populated country of the world, and 7% of its population is above 60 years [3], and this number is predicted to increase upto 27 million by 2050 [3]. The prevalence of dementia in South Asia is 1.9% which suggests that more than 1.5 million people living in Pakistan suffer from dementia and this number is expected to increase [4, 5]. Besides suffering of the subjects and their families, dementia also causes a large socioeconomic burden in countries like Pakistan.

MCI is considered as a pre-dementia stage between normal ageing and dementia [6], and 5-15% of MCI patients become dementia patients [7]. This suggests that if we can identify, characterize and control MCI at an early stage, we may be successful in decreasing the number of dementia cases. Early intervention/attempts to stop MCI may help slow down the progression of MCI. Exercise is considered as one of the non-pharmacological strategies to increase cognitive functioning of MCI patients and is also thought to reduce risk factors (sedentary life style). Several studies have shown that short or acute bouts of aerobic exercise increase attentional resources during cognitively demanding tasks [8, 9] and performance in executive function

(reaction time and attention) [10]. Long-term treatment with aerobic exercise is also known to improve executive functions (as measured using the trail making test (TMT) B, verbal fluency, and task switching) but memory does not improve [11]. Previous studies support that exercise improves cognition of MCI patients, there are still some studies that contradict this notion. Some studies have shown no improvements in cognitive tasks and executive functions with interventions, such as, multi component exercise [12], functional task exercise [13] and resistance training [14]. Tai-chi programs also showed no effects on executive functions but it improved memory [15]. Therefore, the type of exercise may be an important factor to consider.

Previous studies have shown that there are three types of exchanges associated with MCI and Alzheimer's patients: EEG slowness, complexity of the EEG and perturbation in the EEG [16]. The power in low frequency bands (delta 0.5-4 Hz, theta 4-8 Hz) are increased in Alzheimer's and MCI patients while the power in high frequency bands (alpha 8-14 Hz and beta 14–35 Hz) is decreased [17]. Besides the spectral power, approximate entropy (ApEn) has been used to represent complexity or irregularity in the EEG data [18]. Neurocognitive testing is also used commonly in these populations. Combining EEG parameters with neurocognitive tests would provide an in-depth understanding about the mechanisms of any potential effects of an intervention. Therefore, the aim of this study was to assess the short and long-term cognitive effects of aerobic exercise in MCI patients (effects measured through EEG and neurocognitive tests). We hypothesize that aerobic exercise will have both short and long-term positive effects on cognitive function in MCI patients.

Materials and method

Study design

This study is an interventional study conducted in the Railway General Hospital, Rawalpindi Pakistan. The study protocol was approved by the Internal Review Board (approval number IRB-67) at the Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology and Riphah College of Rehabilitation Sciences, Islamabad, Pakistan.

Patient recruitment

We selected the subjects from those patients who visited hospital and were diagnosed as MCI patient by a clinical expert. MCI patients (n= 40) were randomly divided into two groups; aerobic exercise treatment group (n=21) and no-aerobic exercise control group (n= 19). The mean age of the aerobic exercise treated group was 58$\pm$2 years, and the control group was 60$\pm$3 years (Table 1). Patients were diagnosed by applying Mini-mental state examination (MMSE) and Montreal cognitive assessment (MoCA) tests. Keeping in the view the specificity and sensitivity of MMSE and MoCA [19-21] (mentioned in section: "EEG and neurocognitive assessments"), MCI patient were diagnosed by these tests which are powerful diagnostic tests with substantial accuracy. These tests have been proved valid and reliable tests for screening of cognitive functions, not only in MCI, as suggested by several studies [19-21], but also in stroke [22] and Parkinson disease [23]. The inclusion criteria for the patients were: 1) MMSE and MoCA test's score < 25 points, 2) the patient could read and write his or her name in Urdu (local language) and English, 3) physical ability to perform the aerobic exercise plan, 4) adequate visual and hearing capacity to perform neuropsychological testing, and 5) be able to give verbal and written consent.

The exclusion criteria were:1) cognition problems due to other brain pathologies such as stroke, brain tumor, traumatic brain injury, Parkinson's disease or multiple sclerosis, and 2) a history of cardiac disease in the past, epilepsy, any/or any other major diagnosed psychiatric problem, renal failure, or any other systemic disease (Figure 2). The patients should not be taking any drugs which could interfere with cognition such as antidepressants, benzodiazepines or other central nervous system agents. Patients having habits of smoking, alcohol and significant disturbances in sleep were also excluded from the study.

Exercise treatment/intervention protocol

Aerobic exercise treatment

The patients were treated individually with exercise using a treadmill and a stationary bicycle in a physical therapy department (Figure 1). The target heart rate of the patient was recorded, and it should be between 60% and 80% of the maximum heart rate based on the Karvonen formula. The intensity of patient exercise was also monitored and calculated from the heart rate by using Borg's rating of perceived exertion [24]. Each exercise session consisted of a 5-10 minutes warm-up period at the beginning and a 5-10 minutes cool-down period at the end. The aerobics exercise was performed on the stationary bicycle. During the entire exercise session the heart rate and oxygen saturation were monitored continuously by a cardiac monitor. Each exercise session was continued for a pre-determined time, or it was stopped early if the subject's heart rate (calculated by Karvonen formula) became too high or they over-exerted themselves (assessed by Borg's scale). The EEG recordings were done before and after the first session of aerobic exercise to measure the short-term effects. The duration of each session of exercise was aimed to be increased gradually from 20 minutes to 40 minutes, from the first session to the last

session; however, this would depend on the heart rate and exertion response of each individual patient as described above. Aerobic exercise sessions were performed, three days per week by all the participants for six weeks. EEG, MMSE, MoCA, TMT-A and B were recorded before and after six weeks of treatment to measure the long-term effects.

No-aerobic exercise control group

For the no-aerobic exercise control group, no proper exercise treatment was given. Instead only gentle movements and general body stretching were advised to perform at their home. It was recommended that each patient should perform these movements three times per week for six weeks, and follow-up questioning confirmed that this was adhered to. Pre- and post-intervention/control measurements of EEG and neuropsychological testing were performed on these patients as well.

EEG and neurocognitive assessments (MMSE, MoCA, TMT-A and TMT-B)

EEG was recorded before and after the first session of aerobic exercise or stretching session and after six weeks of aerobic exercise training or stretching in both groups. Neurocognitive testing was done only before and after six weeks of training.

EEG validation

Emotiv was used to record EEG in this study. To validate the EEG recordings, EEG was recorded two times on two separate days using the EEG recording protocol described below. The differences between these two separate recordings were analyzed. Slowness and complexity of EEG was calculated, in both eyes open and eyes closed state.

EEG recordings

EEG was recorded using the Emotiv EPOC® Headset with 14 channels (AF3, F7, F3, FC5, T7, P7, O1, O2, P8, T8, FC6, F4, F8, and AF4) and 2 references (according to the International 10-20 electrode location system). The data acquisition parameters were: sampling frequency = 128 Hz, resolution 14 bits (1LSB = 0.51μV), bandwidth = 0.2 to 43 Hz (5th order Sinc Filter, 50 Hz notch). All recordings were performed with electrode impedances below 10kΩ in a noise reduced environment. The total recording time was 2 minutes. During this time the patients alternated between closed their eyes for 30 seconds and then opened their eyes for 30 seconds based on the experimenter's instructions. This process was repeated two times. Patients were seated in a chair and were told not to move their hands, eyes and other parts of the body [25-28].

MoCA and MMSE

For MoCA, the testing procedure was the same as described previously [20, 21] with slight modifications. MoCA is a highly sensitive (80-100%) and specific (56-76%) screening tool for MCI patients [21]. It consisted of 30 points, which cover eight different domains of cognition: visuospatial/executive function, naming, verbal memory registration and learning, attention, abstraction, delayed verbal memory and orientation. Patients with MoCA scores of less than 26, are considered as cognitively impaired. The Urdu version of MoCA was used in this study.

For MMSE, the testing procedure was the same described previously [19, 20] with slight modifications. MMSE is a sensitive (40-60%) and specific (65-90%) tool used for screening of MCI patients. It also consisted of 30 points, covering different domains of cognition. Patients with MMSE scores of less than 25 are considered as cognitively impaired [20]. The MoCA and

MMSE tests were only applied after six weeks of treatment (and not after a single session to avoid a potential learning effect).

TMT-A and TMT-B

TMT-A and TMT-B are used to determine the executive functions (processing speed and task switching), and the testing procedure was same described previously [29, 30], with slight modifications. TMT was performed on a paper using a pen. TMT consists of two sub tests. In TMT-A, the patient has to connect numbers in a sequence by continuing patterns. In TMT-B, the patient has to draw a line switching between letters of the alphabet and numbers in a correct sequence. The time to complete both tasks was recorded. A blinded trained therapist for these tests applied tests before and after the intervention/control. The TMT-A and B tests were only applied after six weeks of treatment, and not after a single session to avoid a potential learning effect.

Data processing

To measure the slowness of the EEG signals, average power of the following frequency bands were calculated: delta (0.5–4 Hz), theta (4–8Hz), alpha1 (8–11 Hz), alpha2 (11–14 Hz), beta1 (14–25 Hz) and beta2 (25–35 Hz). Calculations of relative band spectra of the above mentioned bands were performed using Matlab® 2015. The power across frequencies in the specific band was normalized to the total power in the EEG.

For complexity, the ApEn was calculated and used as a measure of regularity. ApEn is a non-linear statistically valid formula tool that can quantify their regularity of time series. As suggested by Pincus [31] we have used an embedding dimension of two and a tolerance of 0.2 times the standard deviation of the original data. The results of the ApEn have been averaged

based on all the artifact-free frames/epochs within the two-minute period of EEG recordings, during eyes open and eyes close state.

Statistics analysis

Data are reported as mean ± standard error of mean (SEM). Equipment validation was done by comparison of two readings of EEG at two different times, by using paired t-test. To determine the effects of aerobic exercise on slowness and complexity of the EEG, a two-way ANOVA was applied. The factors were "time" (three levels: before treatment, after one session, and after six weeks) and "group" (two levels: aerobic exercise and no-aerobic exercise); this test was repeated for eyes open, eyes close and each EEG measure separately. Potential significant test statistics were followed up using Scheffe's post hoc test. Independent t-tests were used to determine differences for MMSE, MoCA, TMT-A and TMT-B between the aerobic exercise group and no-aerobic group. The results were considered significant only if the "p" value was less than 0.05. All the statistical analyses were performed in SPSS 21.

Results

Equipment validation

Equipment validation was done by comparison of two readings of EEG at two different times. Paired t-test showed that there was no significant difference in the eyes closed state for the delta (0.813 ± 0.018; $p = 0.233$) and theta (0.061 ± 0.007; $p = 0.453$) waves on the first recoding day as compared to delta (0.793 ± 0.019) and theta (0.066 ± 0.006) waves of the second recording day. In the eyes open state, there was no significant difference in delta (0.822 ± 0.019; $p = 0.332$) and theta (0.071 ± 0.008; $p = 0.658$) as compared to the delta (0.808 ± 0.017) and theta (0.068 ± 0.005) waves of the second recording day.

The ApEn of the EEG revealed that there was no significant change (0.474±0.022; p = 0.231) in the eyes closed state on the first recording day as compared to complexity (0.503±0.029) of the second recording day. In the case of eyes open state, there was no significant change in complexity (0.439±0.024; p = 0.095) as compared to complexity (0.455±0.022) of the second reading.

After acute sessions reading there were four drop outs in the aerobic treated group and three drops outs in the no-aerobic group (Figure 2).

Effects of aerobics exercise on slowness of EEG

There was a significant interaction effect of factor "group" and "time "for the delta ($F_{(2,107)}$ = 4.868; p=0.009), alpha2 ($F_{(2,107)}$ = 4.419; p=0.014) and beta1 ($F_{(2,107)}$ = 5.956; p=0.004) in eyes close state (Table 2). In eyes open state there was significant interaction effect of factor "group" and "time" for delta ($F_{(2,107)}$ = 3.880; p=0.024), theta ($F_{(2,107)}$ = 4.578; p=0.012), beta1($F_{(2,107)}$= 3.336; p=0.039) and beta2 ($F_{(2,107)}$ = 4.373; p=0.015; Table 3).

Short-term effects of aerobic exercises on slowness of EEG

There was a significant difference, and that the EEG has become "faster" after one session in delta (0.678±0.035; p=0.015) and beta1 (0.079±0.010; p =0.002) of the aerobic treated group in eyes closed state as compared to delta (0.791±0.033) and beta1 (0.044±0.007) of the no-aerobic control group, while theta, alpha1, alpha2 and beta2 remained unaltered after one session of aerobic treatment (Table 2). In eyes open state, there was a significant difference after one session in delta (0.064±0.029; p=0.022), theta (0.118±0.014; p=0.00004), beta1(0.076±0.009; p=0.013) and beta2 (0.048±0.0008; p=0.001) as compared to the delta (0.769±0.057), theta

(0.048±0.009), beta1 (0.041±0.013) and beta2 (0.026±0.006) of no-aerobic control group, while alpha1 and alpha2 remained unaltered after one session of aerobic treatment (Table 3).

Long-term effects of aerobic exercises on slowness of EEG

There was significant improvement after 18 sessions in delta (0.581±0.036; p=0.005), alpha2 (0.068±0.009; p=0.003) and beta1 (0.010±0.010; p=0.002) of aerobic treated group in eyes closed state as compared to delta (0.723±0.023), alpha2 (0.036±0.007) and beta1 (0.059±0.006) of the no-aerobic control group, while theta, alpha1, and beta2 remained unaltered after 18 sessions of aerobic treatment (Table 2). In eyes open state there was no significant difference after 18 sessions in all waves (Table 3).

Effects of aerobics exercise on complexity of EEG

There was significant interaction effect of factor "group" and "time" for the complexity ($F_{(2,107)}$ = 4.587; p=0.002) in eyes close state. In eyes open state there was significant interaction effect of factor "group" and "time" for complexity ($F_{(2,107)}$= 4.022; p=0.021; Figure3A and 3B). The raw data of EEG recording are shown in figure3C and 3D.

Short-term effects of aerobic exercises on complexity of EEG

The ApEn of the EEG revealed that there was a significant improvement (0.601±0.051; p=0.027) after one session of aerobic exercise as compared to of no-aerobic control group (0.469±0.036) in eyes close sate (Figure3A). In the case of eyes open state complexity was also significantly improved (0.602±0.056;p=0.005) after one session of aerobic exercise treatment as compared to complexity (0.454±0.022) of no-aerobic control group (Figure3B).

Long-term effects of aerobic exercises on complexity of EEG

The ApEn of the EEG revealed that there was significant improvement (0.751±0.051;p=0.001) after six weeks of aerobics exercise as compared to no-aerobic control group (0.533±0.029) in eyes close sate (Figure3A). In the case of eyes open state complexity was not significantly improved (0.515±0.049; p=0.711) after six weeks of aerobic exercise treatment as compared to complexity (0.536±0.029) of no-aerobic control group (Figure3B).

Effects of aerobic exercise on neurocognitive tests

The neurocognitive tests results showed that there was a significant improvement after six weeks in TMT-A (1.407±0.156; p=0.005; Figure 4A), TMT-B (2.803±0.282; p=0.007; Figure 4B) MMSE (26.353±0.469;p=0.032; Figure 5A) and MoCA (22.882±0.401; p=0.036; Figure 5B), of aerobic treated group as compared to TMT-A (2.198±0.208), TMT-B (3.811±0.205), MMSE (24.177±0.849) and MoCA (20.941±0.793) of the no-aerobic control group.

Discussion

Aerobic exercise due to its potential therapeutic effects represent as an emerging candidate for MCI subjects. Although, aerobic exercise is one of the main types of exercises, but to our knowledge its effects on MCI subjects were not explored on slowness and complexity of EEG, particularly short and long-term effects in a single study. A pilot study from our lab [32] encourage us to determine effects of aerobic exercise in MCI patients in detail.

It has been reported that the MCI patient's EEG becomes progressively slow over time compared to a healthy individual [33]. Such "slowing" of EEG appears to be a sensitive measure of changes in cognitive impairment during the early stages of disease progression [33]. Delta waves

powers are increased in MCI patients due to loss of cortico-cortical connectivity [34], but the theta waves are increased due to slowing of subcortical axonal time conduction in MCI Patients [35]. These findings have been suggested to reflect, or represent indicators, of disease progression towards Alzheimer's disease [36]. This loss of cortical connectivity and slowness of reactivity is due to damage of the cholinergic neurons in lateral capsular pathways and Perisylvian pathways. These pathways have a significant role in cortical activity, and thought to be responsible for the "readiness" state [37]. These pathways have dense cholinergic fibers [38]. It has been reported previously that exercise increases neurotransmitters, such as, acetylcholine in brain [39]. Different studies suggested that patients of MCI show a decrease in beta bands intensity. Theta and beta bands powers are the earliest detected changes in MCI patients [40, 41]. Moreover, it has been reported that after aerobic exercise, there is a constant increase in BDNF levels up to 60 minutes [42], helping in improved cognitive function by increasing neural plasticity [43], suggesting the immediate effects of aerobic exercise at molecular level. Other studies have consistently shown that a single bout of physical exercise enhances neuroplasticity [44, 45]. Aerobic stationary bicycling for 30 minutes increases attentional processing and plasticity among frontal, central and parietal midline brain areas [46]. Along with this, aerobic exercise can improve perfusion of various parts of the brain [47, 48]. These above mentioned studies have given clear indication about the immediate effects of exercise on brain. Therefore, the aerobic exercise conducted in our study is likely to have immediate effects in the form of increased levels of acetylcholine, BDNF and cerebral blood flow, which may have caused significant improvement in delta, theta and beta bands after single session and 6 weeks of aerobic exercise treatment.

In the present study the focus was also to determine effect of aerobic exercise on the complexity of EEG. There are various measures one can use to determine the complexity of EEG, including sample entropy [49], ApEn [31], auto-mutual information [50] and Lempel – Zev complexity [51, 52]. In the current study complexity of EEG was measured by ApEn, as this is widely accepted for the diagnosis of cognitive impaired patients [31, 53]. Electrophysiological parameters within the cerebral cortex of Alzheimer's patients are more regular as compared to healthy individuals [53], although the exact mechanism for this regularity is not clear [16]. Neuronal death and loss of neurotransmitter activity have both been suggested as reasons for more regularity or reduced complexity of EEG in Alzheimer's patients [16, 54]. It has been reported previously that exercise increases neuronal plasticity by up-regulating neuronal cell proliferation programs, increasing cerebral blood flow, increasing the permeability of the blood-brain barrier [48], due to angiogenesis and by increasing the number of neurons in transient stage [55, 56]. Our results reveal that aerobic exercises increased the complexity of EEG, not only in the short-term but also as a long-term effect. Previously, it is reported that acute exercises (short-term effects) activates the prefrontal cortex, as there is a direct relationship between cognitive control and oxygenation of prefrontal cortex during exercise [57]. Another study has reported that short bouts of exercise also increase neurophysiological changes, with the key factor being the intensity of the exercise, while exercise duration showed no significant difference [58]. The increased complexity of the EEG observed in the current study following exercise therefore appears to have a positive effect of exercise. It may in the future also be used as a prognostic indicator.

As part of the neurocognitive tests utilized in this study the MoCA, MMSE, TMT-A and B were performed to assess specific executive functions such as visual search, movement speed and

cognitive alteration [29, 59]. Executive functions are compromised or decrease in MCI and Alzheimer's patients [29]. As the brain ages its reactivity integrative ability is thought to decrease. This has for example been shown with decreased values of clustering coefficients (small world index) and path length in older adults as compared to young people [60]. The current study supports these previous findings and extends our knowledge in relation to MCI patients, as it showed that aerobic exercise improved several domains of cognition, such as, alternating trail making, visuo-constructional skills, naming, memory, attention, sentence repetition, verbal fluency, abstraction and delayed recall, as measured by neurocognitive tests. The results of the current study also support another study that found that aerobic exercise improves executive functions [11], behavior performance and cognitive controls. However, such effects have so far only been measured in healthy individuals after three days of exercise [58]. Previously it is reported that physical exercise provide enriched environments, and therefore improves and promotes neurogenesis and synaptogenesis within the hippocampus [55, 56, 61] that prevents the deterioration in brain function and cognition of MCI patients.

Limitations and other considerations

Medication can have multiple side effects and their therapeutic effects may take an extended period of time to eventuate [62]. It is therefore not possible to exclude some medication confounding effects may have occurred in the current study. It is also important to keep in mind that physical activity not only improves cognitive function, but it is also known to provide other health benefits, like positive effects on depression [63], improvement of quality of life [64], decreased risk of falls [65], improved cardiovascular function [66] and decrease disability [67]. Although exercise is non-invasive and is usually without side effects, it should still be planned and carried out under supervision by a trained individual because specific exercises may be

needed for specific individuals, and exercise has the potential to cause damage in certain cases where patients have cardiovascular diseases [68]. An individualized exercise program is recommended, as for example, acute effects of high intensity aerobic exercise is known to decrease executive functions [69]. The sample size of this study was limited, thus the reader should interpret the findings with caution. There were also some drop outs that may have influenced the current findings. Future studies should include a larger sample size. Future studies should also consider using more advanced EEG equipment to determine the mechanism and inter segment pathways of different parts of brain.

Conclusion

An important finding of this study was that cognitive impairment associated with age not only slowed down but it could also be improved with aerobic exercises. This aerobic activity could be performed on a stationary bicycle, treadmill or both. This intervention could be given in any setting, ranging from rehabilitation centers to the home of the individual. It could be concluded that mild to moderate aerobic exercise has both short and long-term positive effects in MCI patients.

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Legends to the figures:

Figure 1: Details of aerobic exercise plan for intervention group.

Figure 2: Flow chart of patients' recruitment and follow-up assessments. MMSE = mini-mental state examination, MoCA = Montreal cognitive assessment, EEG = Electroencephalography, TMT = trail making test.

Figure 3: The graph showing the complexity as approximate entropy (ApEn) of EEG. (A) ApEn of the EEG during eyes close. (B) ApEn of the EEG during eyes open in aerobic exercise treated and no-aerobic exercise group. The p-value was obtained by two-way ANOVA.*p< 0.05, **p< 0.01, ***p< 0.001. (C) Raw data of EEG of no aerobic exercise group shown for a duration of 30 seconds, and from these 30 seconds, 4 seconds are expanded and shown in the lower panel. (D) Raw data of EEG of aerobic exercise treated group shown for a duration of 30 seconds, and from these 30 seconds, 4 seconds are expanded and shown in the lower panel.

Figure 4: The graph showing the trail making test (TMT) A and B. (A) Trail making test-A. (B) Trail making test-B in aerobic exercise treated and no aerobic exercise group. The p-value was obtained by independent t-test. ***p < 0.001.

Figure 5: The graph showing the MMSE and MoCA tests. (A) MMSE. (B) MoCA in aerobic exercise treated group and no exercise group. The p-value was obtained by independent t-test. *p< 0.05.

Figure. 1: Amjad et al., 2018
Aerobic exercises plan

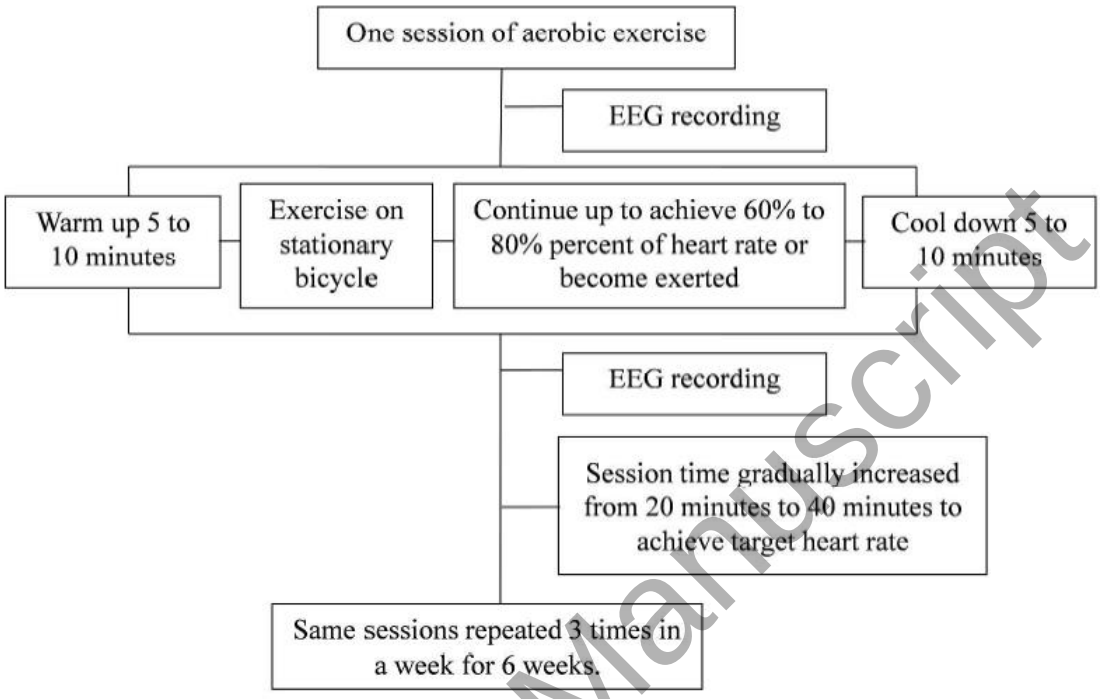


Figure. 2: Amjad et al., 2018
CONSORT diagram of study

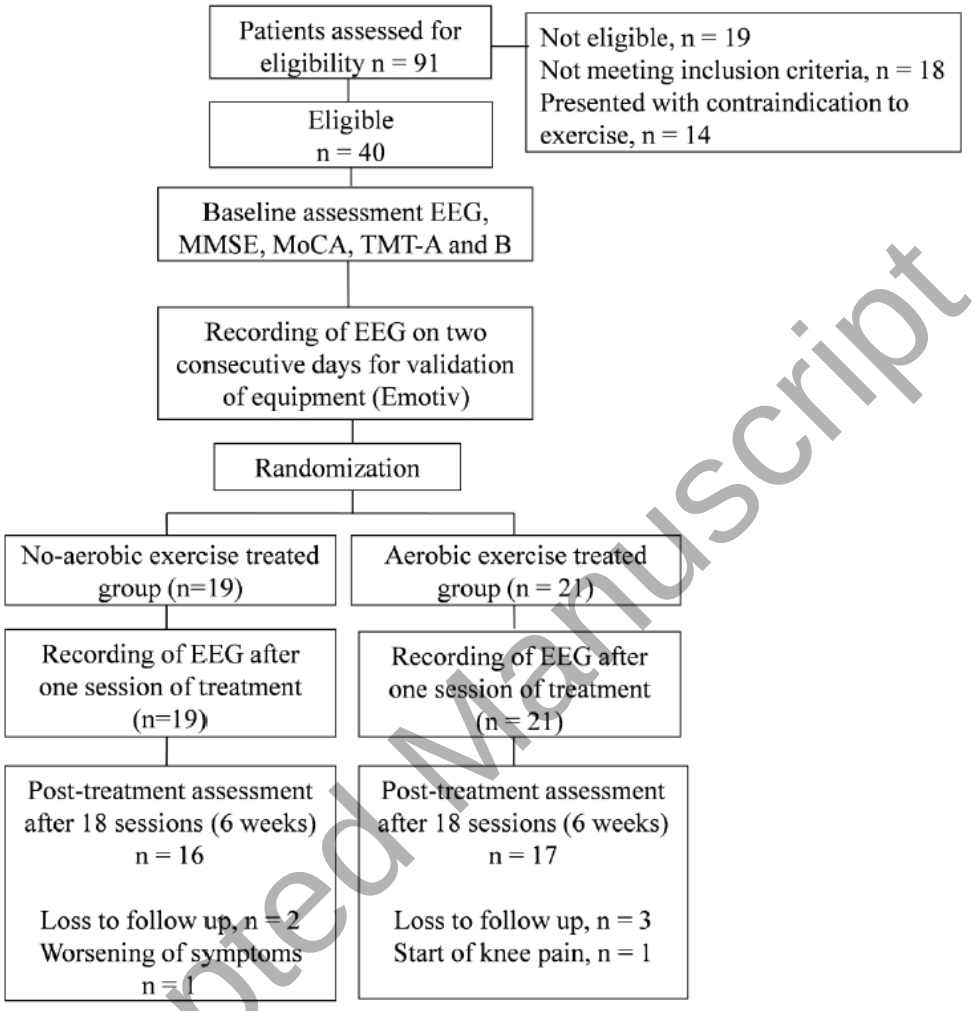
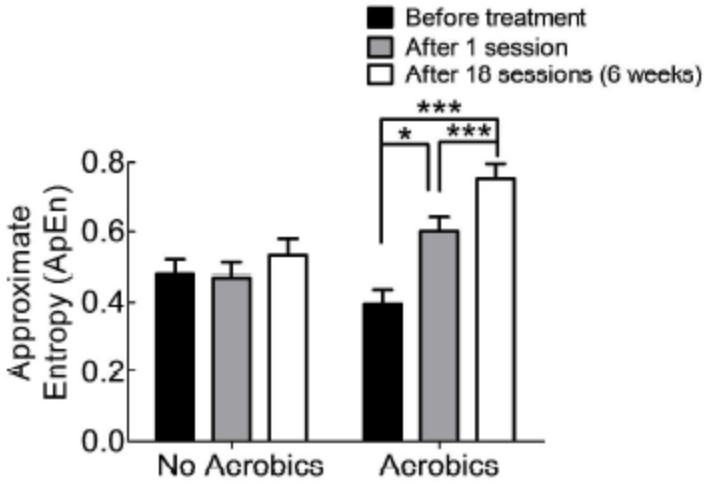


Figure. 3: Amjad et al., 2018

A. EEG complexity (eyes close)



B. EEG complexity (eyes open)

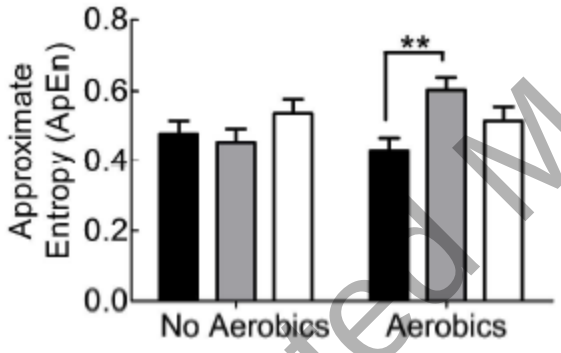


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Figure-3C

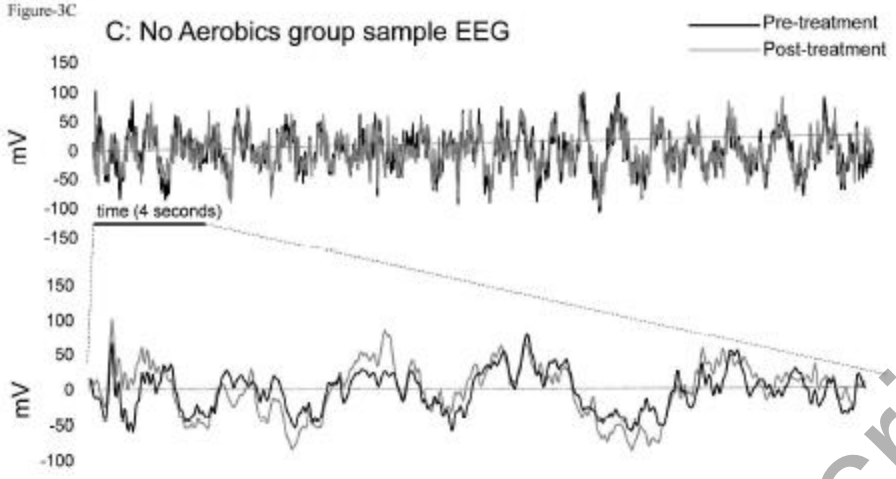

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Figure-3D

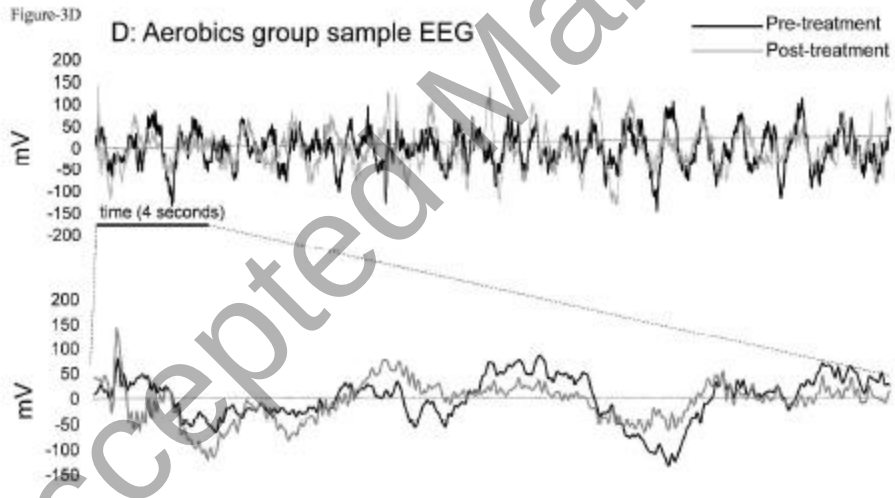

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Figure. 4: Amjad et al., 2018

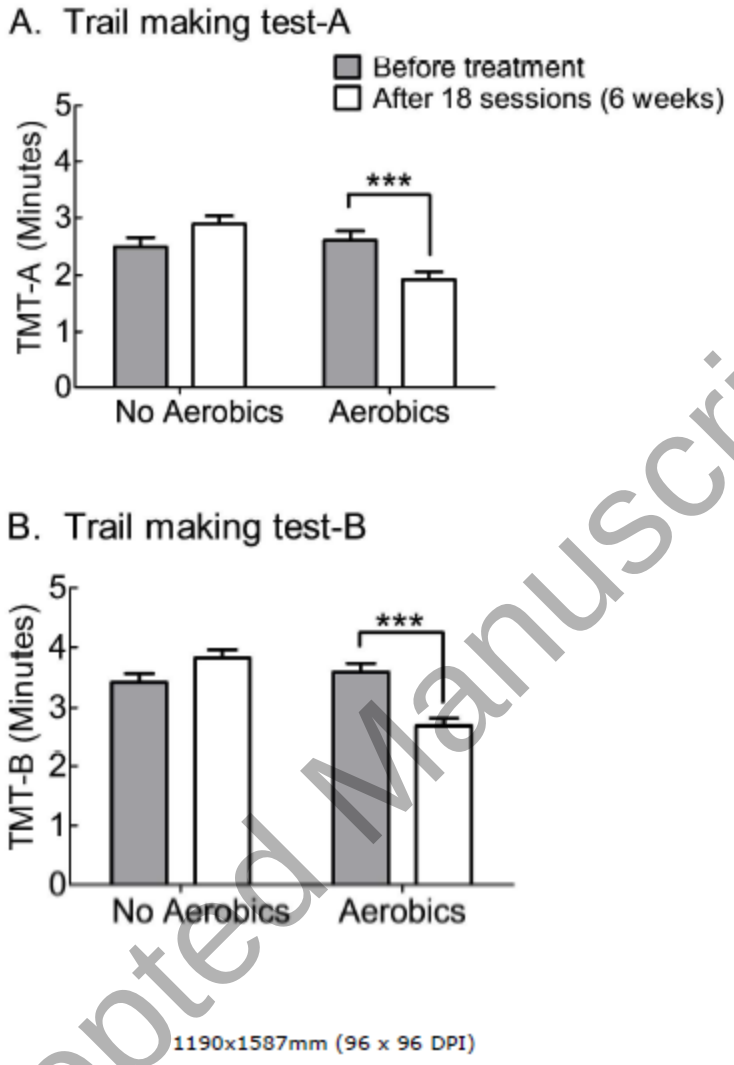

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Figure. 5: Amjad et al., 2018

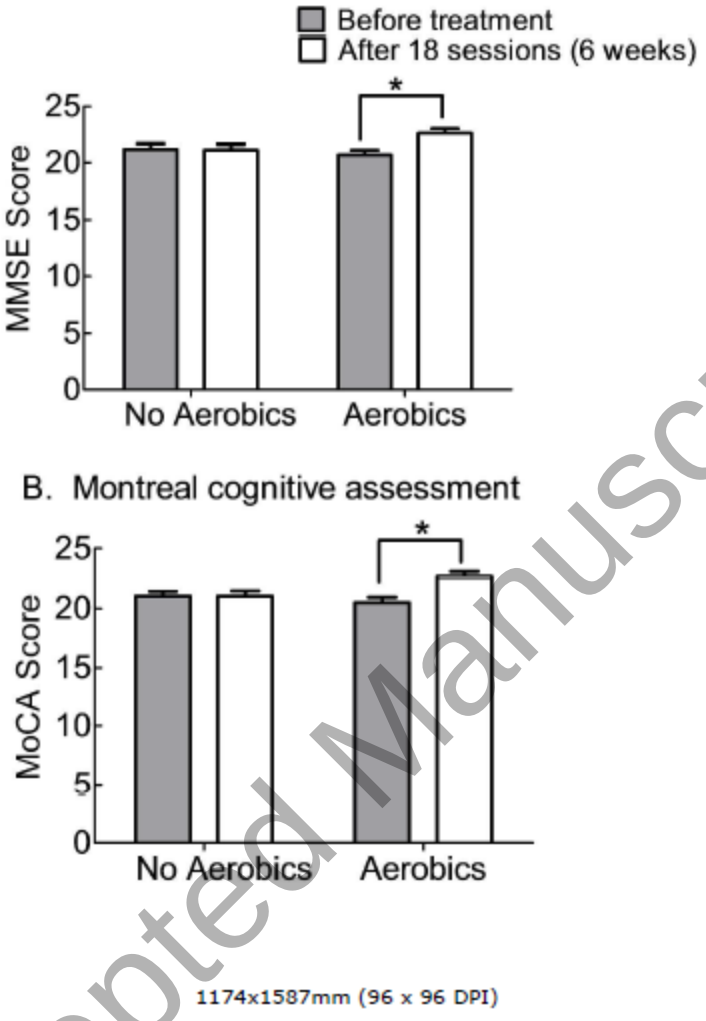

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Table 1: Demographic data of aerobic treated group and no-aerobic exercise group.

Variables	**No-aerobic control group Baseline**	**Aerobic exercise treated group Baseline**
Age (Years), mean ± SD	59.56±2.65	58.23±2.31
Total subjects, n (Females)	19(9)	21(10)
BMI (kg/m^2), mean ± SD	27±2.7	26±3.9

SD= standard deviation, BMI= Basal metabolic index.

Table 2: Data presented as mean ± standard error of mean (SEM). Slowness of EEG (eyes close) in aerobic treated group and no-aerobic control group.

Test variables	**No-aerobic control group**			**Aerobic exercise treated group**			**F Values**	**P values**
	Pre-treatment mean± SEM (n=19)	**After one session mean ± SEM (n=19)**	**After six weeks mean ± SEM (n=16)**	**Pre-treatment mean± SEM (n=21)**	**After one session mean ± SEM (n=21)**	**After six weeks mean ± SEM (n=17)**		
Delta (0.5-4 Hz)	0.766 ±0.042	0.791 ±0.033	0.723 ±0.023	0.815 ± 0.025	0.678±0.035*	0.581±0.036**	4.868	0.009**
Theta (4-8 Hz)	0.069 ±0.011	0.071 ±0.012	0.093 ±0.010	0.065 ± 0.011	0.097 ±.014	0.119± 0.017	1.053	0.353
Alpha 1 (8 - 11 Hz)	0.048 ±0.011	0.046 ±0.010	0.055 ±0.007	0.034 ± 0.006	0.065±0.011	0.077±0.011	2.085	0.129
Alpha 2 (11-14 Hz)	0.033 ±0.008	0.026 ±0.005	0.036 ±0.007	0.023 ±0.004	0.044 ± 0.008	0.068± 0.009**	4.416	0.014*
Beta 1 (14-25 Hz)	0.052 ±0.010	0.044 ±0.007	0.059 ±0.006	0.038 ± 0.006	0.079 ± 0.010**	0.010± 0.012**	5.956	0.004**
Beta 2 (25-35 Hz)	0.052±0.010	0.044±0.007	0.059±0.006	0.038± 0.006	0.079± 0.011	0.105± 0.013	2.527	0.085

The p-value was obtained by two-way ANOVA.*p<0.05, **p<0.01. Significance is shown after comparison with pre-treatment values.

Table 3: Data presented as mean ± standard error of mean (SEM). Shows slowness of EEG (eyes open) in aerobic treated group and no-aerobic control group.

Test variables	No-aerobic control group			Aerobic exercise treated group			F Values	P values
	Pre-treatment mean± SEM (n=19)	After one session mean ± SEM (n=19)	After six weeks mean ± SEM (n=16)	Pre-treatment mean± SEM (n=21)	After one session mean ± SEM (n=21)	After six weeks mean ± SEM (n=17)		
Delta (0.5-4 Hz)	0.761±0.050	0.769±0.057	0.787±0.074	0.847±0.037	0.640±0.029*	0.730±0.033	3.880	0.024*
Theta (4-8 Hz)	0.057±0.011	0.048±0.009	0.059±0.010	0.057±0.011	0.118±0.014***	0.087±0.013	4.578	0.012*
Alpha 1 (8 - 11 Hz)	0.077±0.019	0.050±0.012	0.057±0.016	0.036±0.012	0.069 ±0.050	0.045±0.007	2.676	0.073
Alpha 2 (11-14 Hz)	0.034±0.009	0.498±0.472	0.031±0.006	0.018 ±0.004	0.044±0.006	0.026±0.005	0.896	0.411
Beta 1 (14-25 Hz)	0.046±0.012	0.041±0.013	0.041±0.008	0.033±0.006	0.076±0.009*	0.066±0.011	3.336	0.039*
Beta 2 (25-35 Hz)	0.022±0.006	0.026±0.006	0.018±0.004	0.016±0.003	0.048±0.008*	0.035±0.005	4.373	0.015*

The p-value was obtained by two-way ANOVA.*p<0.05, ***p<0.001. Significance is shown after comparison with pre-treatment values.