2014

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European Journal of
Psychology &
Educational Studies

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A pilot study on the effects of exercise on depression symptoms using levels of neurotransmitters and EEG as markers

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ABSTRACT

Context: The prescribing of exercise by physicians has become a popular practice, yet the effectiveness of exercise on symptoms of depression is difficult to determine due to a lack of randomized controlled trials with clinical populations. Reports also indicate that only a small percentage of physicians advise their patients regarding exercise and confusion still exists as to how much and what types are best. **Aims:** To understand the mechanisms that make exercise a viable treatment in depression. **Settings and Design:** This study employed a six-week, two group, single-level trial, pre- and posttest design using self-report of symptoms, blood levels of serotonin, dopamine, epinephrine, and norepinephrine, and frontal slow wave EEG activity as markers. This study was registered with clinicaltrials.gov. ID# NCT02023281. **Subjects and Methods:** Eleven participants with a diagnosis of depression between the ages of 18 and 65 were enrolled from March 2013 through May 2013. Baseline and post-intervention measures consisted of the Beck Depression Inventory-II, blood serum levels of serotonin, catecholamines (epinephrine, norepinephrine, and dopamine), and mean alpha frequency. **Statistical Analysis Used:** A series of independent t-tests for each dependent variable was conducted. **Results:** Independent t-tests reveal significant between-group differences in depression scores ($P = 0.005$, $d = 2.23$); $F7$ activity ($P = 0.012$, $d = 1.92$); and $F8$ activity ($P = 0.04$, $d = 1.52$). **Conclusions:** The results of this pilot study show that even mild to very moderate levels of exercise 2-3 times per week consisting of alternating days of aerobic and strength resistance training can be effective in reducing symptoms of depression giving physicians concrete information for their patients on the prescription of exercise.

Key words: Depression, exercise, EEG, neurotransmitters

Introduction

The prescribing of exercise by medical practitioners has become a popular practice, yet the effectiveness of exercise on symptoms of depression is difficult to determine due to a lack of randomized controlled trials with clinical populations.[1] Although practice guidelines recommend practitioners to counsel their patients on the benefits of exercise, reports indicate that only a small percentage of practitioners advise their patients regarding exercise and confusion still exists as to how much and what types are best.[2,3] Known effective treatments for depression include cognitive behavioral therapy (CBT) and behavioral activation. Behavioral activation is a combined approach using elements from CBT and behaviorism and has been used for decades.[4,5] The focus of these treatments is to get the patient to do something different in form of cognition, environment, and behavior, and these treatments have shown to substantially reduce

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symptoms of depression.[6] The prescription of exercise for those who struggle with depression can be such an approach.

This study seeks to understand the mechanisms that make exercise a viable treatment in depression by examining self-report of symptoms, blood levels of serotonin, dopamine, epinephrine, and norepinephrine, and frontal slow wave EEG activity as markers. Although these markers have been examined individually in previous studies, to our knowledge this is the only known study that examines each of these components in a single study. Such information can be useful in understanding the overall neurological components of depression and the effects of exercise on the brain in depressed individuals and give physicians concrete information as to the types and quantity of exercise that is needed for positive effect.

Multiple trials, meta-analyses, and reviews have been conducted in the attempt to clarify the use of exercise in depressed patients.[7-11] Just as antidepressant medications increase brain neurogenesis in the hippocampus, research hypothesizes that physical activity will imitate the role of antidepressants.[12,13] Research has also indicated that exercise as a treatment may result in fewer relapses than treatment with the antidepressant sertraline.[14] Preliminary characteristics of the ideal dosage of exercise as a treatment have been researched, although a definitive dose-response curve has yet to be produced. Research also suggests a natural asymmetry in frontal lobe alpha frequency, with previous researchers reporting that it is common to see higher amplitude alpha activity (8 – 12 Hz) in the prefrontal right hemisphere as opposed to the left hemisphere in non-depressed individuals and the reverse in depressed individuals.[15] Other studies have also supported this assymetry.[15-17]

Built upon the vast array of literature highlighting the association between depression and lowered neurotransmitter levels, research studies are now using neurotransmitter measurements as a marker for depression.[18-22] Although there are no established norms for neurotransmitter levels, the correlation between depression and neurotransmitter levels has been well studied. In correlation with non-depressed individuals, depressed individuals have been found to have raised plasma catecholamine levels, including norepinephrine, epinephrine, and dopamine, high free-serotonin levels and low platelet-serotonin levels;[23-26] however, the findings regarding neurotransmitter changes during exercise have been inconsistent.[27]

Subjects and Methods

This study was funded by Liberty University and reviewed and approved through the Centra Health and Liberty University IRB process. It has also been registered with clinicaltrials.gov (ID# NCT02023281). The study employed a randomized two-group, single-level trial pre- and posttest design consisting of a total of 11 participants with a diagnosis of depression. Diagnosis was confirmed using the Structured Clinical Interview for Axis I Disorders (SCID-I). Baseline and post-intervention measures consisted of the Beck Depression Inventory-II (BDI-II), blood serum levels of serotonin, catecholamines (epinephrine, norepinephrine, and dopamine), and mean alpha frequency. Alpha frequency data were measured using the international 10 – 20 system at locations F1, F2, F3, F4, F7, and F8. Blood serum kits were provided by Centra Health and analyzed at Lab Corp.

Participants diagnosed with major depressive disorder were recruited from general advertisement and patient referral from Centra Health's Occupational Health practice and psychiatric practices within Central Virginia. All individuals were risk-stratified and only those determined to be low risk in accordance to the American College of Sports Medicine[28] were included in the study and subsequently randomly assigned to two groups for six weeks: (a) Structured exercise regimen and (b) an alternate group (control) with no exercise. Both groups were advised to continue with their current modes of intervention as prescribed by their medical or mental health provider, particularly the control group, which was not exposed to the intervention. Those deemed to be at risk for suicide were excluded. Due to time limitations with lab personnel and potential participants leaving at the end of the academic year, only a sample of 13 participants was able to be obtained. Of the 13 participants, two voluntarily withdrew due to a change of mind. The remaining 11 participants were randomly assigned into the exercise (*n* = 5) and control groups (*n* = 6).

Once screening had taken place and participants selected, arrangements were made for participants to collect pretest data. Blood was collected from Centra Health's Health Works, Occupational Medicine practice. EEG data and BDI-II scores were collected in the Liberty University Psychology Lab. Baseline fitness data were collected at the Liberty University Kinesiology Lab. Participants in the experimental group were required to come to the lab 2 – 3 days a week for 30 – 40 minutes for six weeks. At the end of the six weeks, the same data from baseline was collected.

Eligible participants included males and females between the ages of 18 – 65. Participants needed to meet DSM-IV criteria for major depressive disorder. Participants with co-morbidity were required to carry major depressive disorder as a primary diagnosis. Participants needed to be in good medical health or, if having chronic medical conditions, these conditions needed to be currently stable. Participants were allowed to be on common medications for depression provided they had been on a stable dose for at least three months and were still symptomatic. Exclusion criteria included not having major depression as a primary diagnosis, pregnancy, planning to become pregnant, and having a chronic medical condition where exercise would be contraindicated. Other exclusion criteria included if the participant was clinically judged by the investigator to be at risk for suicide or having attempted suicide within the past 12 months. At the end of the study, participants within the alternative group were given a prescription of exercise identical to that of the exercise group.

Procedures for exercise

During the training sessions, participants completed both an aerobic training portion and a resistance training portion of the session. The participants were trained in the Human Performance Lab three days per week on non-consecutive days. Participants alternated between Training Session A and Training Session B for the duration of the six-week training cycle. All training sessions were supervised by a lab assistant.

Training Session A: Subjects completed 30 minutes of cardiovascular (CV) training. For the CV training, the subjects could choose to use either a treadmill, cycle ergometer or a rowing ergometer. The intensity was set at 40 – 59% of heart rate reserve (HHR). After the CV training, subjects completed the resistance training, which consisted of 2 – 3 circuits of 8 – 12 repetitions of the following exercises: Turkish get-ups, step-ups, kettlebell swings, push-ups, and single arm kettlebell rows.

Training Session B: Subjects completed 20 minutes of CV training. The intensity was set at 60 – 89% of HHR. After CV training, subjects completed resistance training, which consisted of 2 – 3 circuits of 8 – 12 repetitions of the following exercises: Plank holds, burpees, lunges, glute bridges, overhead presses using kettlebells, and pull-ups using bands for assistance as needed.

In the event of any medical or mental health emergency, participants would be escorted to the university medical office staffed by Centra Health located down the hall from the exercise lab. From there, the participant would be further assessed and their primary care provider contacted. In the event of a medical or mental health emergency outside of direct participation, participants were directed to follow normal channels of communication with their primary care provider.

Power and sample size calculations

Although a sample size of 20 was expected for achieving a level of power that is greater than 0.70, due to time constraints, only a sample of 11 was able to be obtained but power was still found to be sufficient for a pilot study.

Results

Analyses were completed using the statistical software package SPSS Version 21. Prior to analyses, independent *t*-tests confirmed that the two groups were not significantly different on any of the dependent pretest measures at the outset of the study (with *P* values ranging from 0.18 to 0.99). As for demographic variables, the groups were not significantly different in age, t (9) =0.925, P = 0.38; gender, χ^2 (1, N = 11) =0.110, P = 0.74; or medication use, χ^2 (1, N = 11) =1.061, P = 0.303.

Since individual change on dependent variables for each condition was of primary interest, individual gain scores were calculated for all participants by subtracting the pretest scores from the posttest scores; as long as certain conditions are met (such as high pretest reliability), gain scores serve as an appropriate outcome variable.[29]

In order to examine group differences, a series of independent *t*-tests for each dependent variable was conducted. See Table 1 for gain scores, *t* statistics, and effect sizes (Cohen's *d*) for the two groups. Overall, three significant between-group differences were found. There was a significant between-group difference in depression scores, t (9) = −3.68, P = 0.005, where patients in the exercise condition experienced a significant decrease in depressive symptomatology, as reported on the BDI, compared to controls. By Cohen's[30] standards, the effect size for this difference (d = 2.23) was quite large. In addition, there was a significant difference in *F7* activity, t (9), -3.13, P = 0.012. Participants in the exercise group experienced a decrease in *F7* activity, while control participants experienced an increase, with a large effect size (d = 1.92). Finally, there was a significant between-group difference in *F8* activity, t (9), -2.40, P = 0.04, such that the exercise participants decreased in *F8* activity, while the control participants showed increased activity, again with a large effect size (d = 1.52). Between-group differences for all other dependent variables were not significant.

No significant differences were found in the markers of norepinephrine, epinephrine, serotonin, or dopamine. Note that these markers were measured via blood serum, which does not measure neurotransmitter availability within the synaptic gap. Such assessment would require measurement via cerebral spinal fluid (CSF). This can be considered a limitation of the study, however, measurement with the use of CSF would be considered invasive and not appropriate for this particular study.

Discussion

Exercise has been shown to be effective in improving mood, but the mechanisms that underlie these changes and the specifics regarding type and frequency of exercise remain unclear.[31-33] In an effort to address some of these ambiguities, this study discovered that participants in the exercise group had a significant improvement in depressive symptomatology, as evidenced by decreased BDI scores in comparison to the control group [Figure 1]. The BDI-II scores of the exercise group decreased significantly from 30.8 to 6.8, which amounts to a 78% decrease in BDI-II scores. Similar findings were discovered using behavioral activation in the treatment of depression.[6] While this latter intervention is significant, the findings from this study not only link the emotional benefits of exercise, it provides physicians with more specific information as to the amount of change (exercise) that is needed to effect such results.

Additionally, in an effort to correlate these findings with EEG changes by examining the marker of frontal alpha activity, the exercise group showed a significant decrease in frontal alpha activity measured at F7 in comparison to the control group, which is a 15.7% decrease from pretest (5.1Hz) to posttest (4.3Hz) [Figure 2].

A significant difference was also discovered at F8 between the exercise and control groups with the control group showing an increase in F8 activity pretest (4.2Hz) and posttest (5.6Hz) or a – 23.8% difference [Figure 3]. However, no significant differences were found in alpha activity across the prefrontal cortex. These results are somewhat consistent with the previous research indicating a left frontal bias in people with depression;[16-18] however, these results were not able to replicate the significance of previous studies.

Additionally, the intervention group appeared to have differences in serum serotonin (5HT) and serum norepinephrine (NE) group means, with a smaller increase in serum 5HT levels after the intervention

| Table 1: Mean, standard deviation, *t* statistics, and effect size for dependent variables								
Measure	Pre-test		Post-test		Gain score		*t*	*d*
	M	SD	M	SD	M	SD		
Depression								
Exercise (*n*=5)	30.8	6.6	6.8	6.7	−24.0	9.3	−3.68**	2.23
Control (*n*=6)	29.7	10.1	26.2	13.2	−3.5	9.1		
Norepinephrine								
Exercise (*n*=5)	406.4	322.4	466.6	209.3	60.2	196.0	−1.14	0.69
Control (*n*=6)	286.2	61.1	488.2	240.0	202.0	212.1		
Epinephrine								
Exercise (*n*=5)	45.6	24.1	28.0	6.4	−17.6	28.1	−2.06	1.23
Control (*n*=6)	43.2	39.5	56.7	41.4	13.5	22.2		
Serotonin								
Exercise (*n*=5)	10.6	7.0	15.2	7.0	4.6	9.3	−1.49	0.87
Control (*n*=6)	44.8	52.9	64.8	65.9	20	23.3		
Dopamine								
Exercise (*n*=5)	14.2	7.8	13.2	4.3	−1.0	8.9	−1.57	0.95
Control (*n*=6)	11.3	3.8	18.0	6.9	6.7	7.3		
F1								
Exercise (*n*=5)	5.5	1.3	4.6	0.39	−0.84	1.2	−1.24	0.73
Control (*n*=6)	5.5	1.3	5.5	1.6	0.0	1.1		
F3								
Exercise (*n*=5)	5.5	0.80	4.7	0.50	−0.76	0.8	−1.27	0.76
Control (*n*=6)	5.7	1.2	5.6	1.9	−0.07	1.0		
F7								
Exercise (*n*=5)	5.1	0.90	4.3	0.40	−0.78	0.68	−3.13*	1.92
Control (*n*=6)	4.6	1.3	5.4	1.8	0.83	0.97		
F2								
Exercise (*n*=5)	4.7	1.2	4.6	0.10	−0.1	1.2	−0.286	0.17
Control (*n*=6)	5.4	1.3	5.4	1.5	0.08	0.95		
F4								
Exercise (*n*=5)	5.3	0.90	4.6	1.0	−0.70	1.1	−0.958	0.60
Control (*n*=6)	5.5	1.2	5.6	1.7	0.02	1.3		
F8								
Exercise (*n*=5)	4.2	0.70	4.0	0.45	−0.16	0.63	−2.40*	1.52
Control (*n*=6)	4.2	0.90	5.6	1.7	1.3	1.2		
* *P*<0.05; **P*<0.01, SD: Standard deviation								
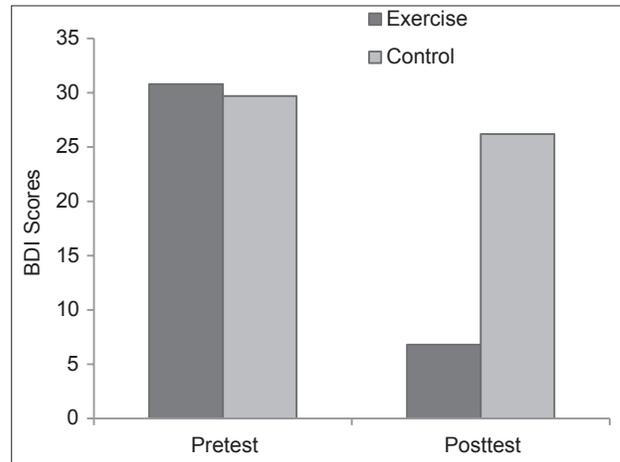
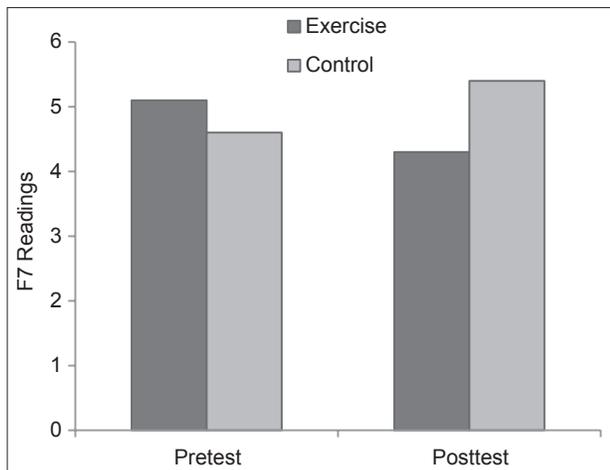**Figure 1:** Depression scores by group and testing time

Figure 2: F7 readings by group and testing time
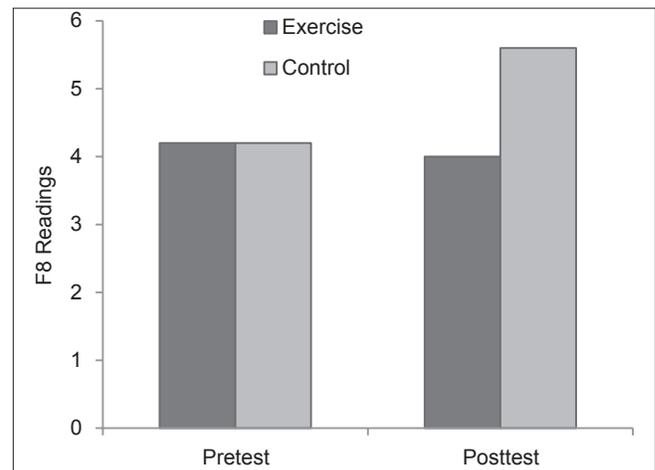

Figure 3: F8 readings by group and testing time

compared to the control group, and a smaller increase in serum NE following intervention compared to the control group. Although these results did not prove to be significant markers, patients with major depression have been shown to exhibit greater sympathetic responsiveness correlated with increased NE and high parasympathetic activity correlated with increases in free 5HT.[24] The smaller decrease in serum 5HT may be the result of changes in platelet aggregability and the subsequent retention or release of 5HT. Emotional state and physical activity have been shown to result in changes in sympathetic nervous system activation correlating with decreases in plasma catecholamines; additionally, regular exercise has also been correlated with inhibition of platelet aggregability that may be further correlated with alterations in 5HT levels in the blood.[34,35] Although this study was not able to replicate the degree of findings from previous studies examining catecholamine and 5HT levels,[20,21,25-28] this study did show a reduction in serum levels of catecholamine and 5HT levels within the exercise group; however, these decreases were not significant. On preliminary review of the data in this study, given the improvements in group mean BDI scores and serum 5HT and NE levels in the exercise group compared to the control group, the present research suggests that adherence to an individualized exercise regimen is indeed correlated with improvement in symptoms of depression and further correlated with decreased levels of serum NE and 5HT when compared to a control group.

Conclusion

The purpose of this research was twofold, to address some of the questions of previous researches regarding the types of exercise that can be effective in the treatment of depression and to give medical practitioners clearer direction to advise their patients on the specifics of exercise and its benefits in their depressed patients. The main limitations of this study are the small sample and the method of neurotransmitter analysis. Although blood serum levels are a common method of sampling and analysis, this method does not provide enough information as to their effects in the brain as they pertain to mood but must be explained through the body's synthesis of serotonin and catecholamines with and without exercise. A more comprehensive analysis would necessitate collection of CSF, which would be an invasive procedure. However, the results of this pilot study show, particularly through the use of self-report, that even mild to very moderate levels of exercise 2-3 times per week consisting of alternating days of aerobic and strength resistance training can be effective in reducing symptoms of depression. These results are magnified by the high effect sizes.

Acknowledgement

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