Efficacy of Exercise in Reducing Depressive Symptoms across 5-HTTLPR Genotypes

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ABSTRACT

RETHORST, C. D., D. M. LANDERS, C. T. NAGOSHI, and J. T. D. ROSS. Efficacy of Exercise in Reducing Depressive Symptoms across 5-HTTLPR Genotypes. Med. Sci. Sports Exerc., Vol. 42, No. 11, pp. 2141–2147, 2010. Introduction: Exercise is effective in the alleviation of depressive symptoms and may have physiological effects similar to those of selective serotonin reuptake inhibitors (SSRI). Recent research has identified the difference in treatment effects across genetic polymorphisms of the serotonin transporter polymorphic region (5-HTTLPR), in which the l allele has been associated with a better response to SSRI compared with the s allele. The purpose of the current research was to examine the antidepressant effects of exercise across 5-HTTLPR genotypes. Methods: Participants, ages 18–23 yr, were randomly assigned to a 5-wk exercise intervention or a no-treatment control group. Participants completed the Beck Depression Inventory before and after the intervention and provided a saliva sample for DNA analysis. Results: Exercise resulted in a significant reduction in depressive symptoms compared with the control group. In addition, individuals with at least one l allele demonstrated greater reductions in depressive symptoms compared with ss individuals. Conclusions: The effects of exercise on depressive symptoms appear to be moderated by 5-HTTLPR genotype, suggesting that the mechanisms responsible for the alleviation of depressive symptoms are similar for exercise and SSRI treatment. Furthermore, these findings suggest that 5-HTTLPR genotype should be a factor in determining the proper line of treatment for depression. Key Words: PHYSICAL ACTIVITY, DEPRESSION, SEROTONIN TRANSPORTER GENE, NEGATIVE LIFE STRESS

Depressive disorders have become a widespread health concern throughout the world. The Global Burden of Disease project ranked depressive disorders fourth in terms of global burden (30). In the United States, the National Institute of Mental Health estimated the costs associated with depressive disorders at $26 billion annually. Even in individuals that do not meet the diagnostic criteria for major depression, depressive symptoms have adverse effects. Minor depression and subsyndromal depression have been associated with an increased risk of major depression, function impairment (24,41), higher rates of disability (4), and increased social dysfunction (16,17).

In addition to the escalating costs associated with treatment of depressive disorders, the accessibility and effectiveness of these treatments limit their impact. Only 55% of people afflicted with a depressive disorder are receiving treatment, whereas alleviation of depressive symptoms is seen in only 32% of those receiving treatment (1). Randomized trials have shown the effectiveness of three classes of treatment to be effective in alleviating depressive symptoms: antidepressants, psychotherapy, and electroconvulsive therapy (31). Despite the empirical evidence demonstrating the effectiveness of these treatments, response rates for antidepressants (37,46,47), psychotherapy (9), and ECT (35) indicate that a large number of individuals do not respond to these treatments. These statistics indicate the need for more cost-effective, accessible, and alternative treatments for depressive disorders. Exercise is one potential treatment that has been supported through research.

Several meta-analyses have been conducted to examine the effects of exercise on depressive symptoms (6,33). The effect sizes of these meta-analyses ranged from 0.53 to 0.88, indicating a moderate to large effect. Despite the moderate to large effect sizes, these studies can be criticized for including studies of poor methodological integrity, such as quasi-experimental trials and cross-sectional studies. Three recent meta-analyses have addressed this criticism by including only randomized controlled trials (28,36,43). With effect sizes ranging from 1.05 to 1.39 within clinical populations, these meta-analyses provide support for the use of exercise in the treatment of depression. Within the general population, an observed effect size of 0.66 (36) indicates that exercise results in a moderate decrease in depressive symptoms in nonclinical populations.

A recent trend in research has been to identify individual differences in response to treatments. One area of examination has been the difference in treatment effects across genetic polymorphisms of the serotonin transporter gene. The
serotonin transporter polymorphic region (5-HTTLPR) is characterized by two alleles, long (l) and short (s) (22), and has been associated with several potential physiological mechanisms that may influence the serotonergic system. The s allele is associated with a lower transcription rate of the serotonin transporter (5-HTT) (13), a decrease in 5-HT metabolism (48), and a lower 5-HTT1A receptor density and receptor binding potentials (7). These alterations within the serotonergic system could potentially increase the likelihood of depression (34). Furthermore, the s allele has been associated with a blunted response to selective serotonin reuptake inhibitors (SSRI) (39). It has been suggested that the lower transcription rates (13,22) and the decreased 5-HT binding sites (32) associated with the s allele may be responsible for this blunted response to SSRI treatment (21).

SSRI act on the serotonergic system by inhibiting 5-HTT and thus decreasing the reuptake of 5-HT from the synaptic cleft (8). SSRI treatment has been associated with decreases in platelet, plasma, serum, and whole-blood serotonin levels (10,14,18,28,29). Likewise, exercise results in a decrease in serum 5-HT (49). In addition, decreases in 5-HT2A receptors have been observed following both SSRI treatment (27) and exercise (44). Considering these similarities, it is plausible that the effect of exercise on depressive symptoms across 5-HTTLPR genotypes will be similar to that of SSRI.

The purpose of the current research was to examine the antidepressant effects of exercise across 5-HTTLPR polymorphisms. It is hypothesized that the exercise intervention will result in a decrease in depressive symptoms compared with a no-treatment control group. Considering the similar effects of SSRI and exercise on the serotonergic system, it is hypothesized that exercise will have effects similar to SSRI on depressive symptoms across 5-HTTLPR genotypes. It is therefore hypothesized that exercise will result in a greater decrease in depression scores in individuals with at least one l allele.

**METHODS**

**Participants.** Participants were recruited in January 2008 from undergraduate kinesiology classes and received extra credit at their instructor’s discretion for their participation. Both men and women, ages 18–23 yr, were included in the study. Before participation in the study, participants completed an informed consent form, which was approved by the university’s institutional review board, and a health history questionnaire. To be eligible for participation, individuals were required to be physically able to exercise, determined by a health history questionnaire. Potential participants were excluded from the study if they were currently being treated for a psychiatric condition. To assess the effectiveness of the exercise intervention on depressive symptoms, a power analysis revealed that 60 participants are needed to achieve a power of 0.80 on the basis of an effect size $d = 0.66$. The effect size in the power analysis was based on a meta-analysis that estimated an effect size of $d = 0.66$ for an exercise intervention on depressive symptoms in a healthy population (36). However, a larger sample was recruited to guard against participant attrition and to detect the difference in effect across 5-HTTLPR genotypes. Participants received extra credit at their instructors’ discretion for their participation in the study.

**Measures.** At pretest, participants completed the Beck Depression Inventory (BDI) (3), the Life Experiences Survey (LES) (38), and the Multidimensional Scale of Perceived Social Support (MSPPS) (51). For DNA analysis, a saliva sample was collected using the Oragene DNA Self-Collection kits (2-mL collection tubes) (DNA Genotek). A 0.5-mL aliquot was removed from each vial for isolation of genomic DNA following the manufacturer’s protocol. Before amplification, purified genomic DNA was analyzed by spectroscopy and agarose gel electrophoresis to determine concentration and overall quality. Using previously described methods (11), primers for the promoter region of 5-HTT were used in a polymerase chain reaction that amplified either the long, l allele, which yields a 419-bp product (16 repeats), or the short, s allele, which yields a 375-bp product (14 repeats). Reaction conditions were as follows: 1× Pfx Amplification Buffer (Invitrogen, Carlsbad, CA), 1× PCR Enhancer Solution (Invitrogen) 1.5 mM of MgSO4, 0.3 mM of dNTPs, 0.1 µM of each primer, 50 ng of genomic DNA, and 1 U of Pfx DNA Polymerase (Invitrogen). Polymerase chain reaction was performed on a PTC-225 DNA Engine (MJ Research, Waltham, MA) after an initial denaturation step of 15 min at 95°C using 35 cycles of the following: denaturation at 94°C for 30 s, annealing at 60°C for 30 s, extension at 68°C for 40 s, followed by a final extension at 68°C for 15 min. Polymerase chain reaction products were analyzed by agarose gel electrophoresis.

**Exercise intervention.** After the initial data collection, individuals were randomly assigned by the lead author using a random numbers table to either an exercise intervention or a no-treatment control group. Participants selected for the exercise intervention group were required to attend three exercise sessions per week for 5 wk. Each exercise session consisted of 30 min of cycling on a stationary bicycle at 60%–70% of the age-based theoretical maximum heart rate ($HR_{max} = 220 - age$). Heart rate was monitored using 810i Polar heart rate monitors (Kempele, Finland). The exercise dose used was based on the findings of Rethorst et al. (36), who demonstrated that the greatest effect on depressive symptoms was associated with moderate intensity exercise of 30–45 min, three times per week. After the completion of the 5-wk exercise intervention, participants from both the exercise and the control groups were asked to once again complete the BDI, the MSPSS, and the LES.

**Statistical analysis.** After the exercise intervention, an effect size, Cohen’s $d$, was calculated to quantify the post-test difference in BDI score between the exercise and the control groups. Cohen (5) provides criteria for categorization of effect size classifying an effect size of 0.20 as
small, 0.50 as moderate, and 0.80 as large. Finally, a series of ANOVAs were conducted to examine the effects of exercise on depression within the entire population, across 5-HTTLPR genotype, and across gender. A mixed $2 \times 2$ (group $\times$ time) ANOVA was used to analyze the effect of the exercise intervention on depressive symptoms. A mixed $3 \times 2 \times 2$ (genotype $\times$ exercise group $\times$ time) ANOVA was used to analyze the effect of the exercise intervention across 5-HTT genotypes. An additional $2 \times 2 \times 2$ ANOVA was conducted with the only two genotype groups (ll/ls vs ss). After the identification of a significant three-way interaction in this analysis, a $2 \times 2$ (genotype $\times$ time) ANOVA was run separately for each treatment group to examine differences in treatment response across genotypes.

RESULTS

One hundred seventy-one participants were assessed before the intervention. The genotype frequencies were not significantly different from the Hardy–Weinberg equilibrium ($X^2 = 0.058$, $P > 0.05$), which tests for expected genotype distribution. After the preintervention assessment, 70 participants were assigned to the exercise intervention, while the remaining 101 participants were assigned to the no-treatment control group. One hundred twenty-nine participants completed the intervention phase, 64 in the control group and 65 in the exercise group. Within the exercise group, 67 of the 70 (95.7%) participants completed the exercise program; three participants did not complete the exercise program (two due to illness and one discontinued exercise without giving a reason). Furthermore, two participants that completed the exercise program failed to complete the postintervention questionnaires. Among those who completed the exercise program, participants attended an average of 11.8 exercise sessions. Of those 101 participants assigned to the no-treatment control group, 64 responded to e-mail requests for measurement at posttest (Fig. 1). There was no

<table>
<thead>
<tr>
<th>Measure</th>
<th>Group</th>
<th>Pretest</th>
<th>Posttest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression (BDI)</td>
<td>Control</td>
<td>5.33 (4.91)</td>
<td>6.20 (5.38)</td>
</tr>
<tr>
<td>Range: 0–30</td>
<td>Exercise</td>
<td>4.60 (3.55)</td>
<td>3.12 (2.90)</td>
</tr>
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<td>Negative life stress (LES)</td>
<td>Control</td>
<td>6.22 (5.00)</td>
<td>5.98 (5.26)</td>
</tr>
<tr>
<td>Range: 0–26</td>
<td>Exercise</td>
<td>5.69 (5.41)</td>
<td>5.49 (5.24)</td>
</tr>
<tr>
<td>Social support (MSPSS)</td>
<td>Control</td>
<td>69.66 (11.57)</td>
<td>69.33 (12.85)</td>
</tr>
<tr>
<td>Range: 13–84</td>
<td>Exercise</td>
<td>72.86 (8.38)</td>
<td>68.26 (17.26)</td>
</tr>
</tbody>
</table>
difference in pretest measurements between those who completed postintervention and those that did not, $F(1, 100) = 1.198$, $P = 0.276$.

Effect of exercise intervention on depression score. Descriptive statistics for preintervention measures of depression, negative life stress events, and social support can be found Table 1. Posttest descriptive statistics are included in Table 1. Mixed $2 \times 2$ (group $\times$ time) ANOVAs revealed nonsignificant group $\times$ time interactions for negative life stress, $F(1, 127) = 0.004$, $P > 0.05$, and social support, $F(1, 127) = 2.253$, $P > 0.05$. The main effect for time was also nonsignificant for both negative life stress, $F(1, 127) = 0.212$, $P > 0.05$, and social support, $F(1, 127) = 2.998$, $P > 0.05$.

The two groups did not differ significantly in depression score at pretest, $t(127) = 0.966$, $P > 0.05$. The $2 \times 2$ (group $\times$ time) ANOVA revealed a significant interaction, $F(1, 127) = 16.816$, $P < 0.01$, indicating that the exercise group experienced a significant reduction in depression score compared with the no-treatment control group (Fig. 2). The effect size for reduction in depression (Cohen’s $d$) was $-0.62$, indicating a moderate to large effect of exercise compared with the no-treatment control.

Effect of exercise on depression across 5-HTTLPR genotypes. Descriptive statistics by genotype are included in Table 2. A mixed $3 \times 2 \times 2$ (genotype $\times$ exercise group $\times$ time) was used to analyze the effect of the exercise intervention across 5-HTT genotypes. The three-way interaction approached significance, $F(1, 124) = 2.758$, $P = 0.067$. However, the distribution of genotypes was not consistent across the treatment groups, putting the analysis at risk because of multicollinearity. To address this concern, the $ls$ and $ll$ genotypes were grouped together (Table 3) because of their similar response to exercise, and an additional $2 \times 2 \times 2$ ANOVA was conducted.

Results of the $2 \times 2 \times 2$ ANOVA revealed a significant three-way interaction, $F(1, 125) = 4.836$, $P = 0.030$, indicating that the effect of exercise varied across genotype. To follow-up on the significant three-way interaction, a $2 \times 2$ (genotype $\times$ time) ANOVA was run separately for each treatment group. Within the exercise group, the ANOVA revealed a significant three-way interaction, $F(1, 125) = 4.836$, $P = 0.030$, indicating that the effect of exercise varied across genotype. To follow-up on the significant three-way interaction, a $2 \times 2$ (genotype $\times$ time) ANOVA was run separately for each treatment group. Within the control group, the genotype $\times$ time interaction, $F(1, 62) = 1.610$, $P > 0.05$, and the time main effect, $F(1, 62) = 0.303$, $P > 0.05$, were not significant.

DISCUSSION

As hypothesized, the exercise intervention was effective in decreasing depressive symptoms compared with a no-treatment control. The effect size of 0.62 is nearly identical

### TABLE 2. Pretest and posttest depressive symptoms by 5-HTTLPR genotype.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Group</th>
<th>Pretest BDI</th>
<th>Posttest BDI</th>
</tr>
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<tbody>
<tr>
<td>$ll$</td>
<td>Control ($n = 24$)</td>
<td>4.79 (4.52)</td>
<td>5.98 (5.04)</td>
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<td></td>
<td>Exercise ($n = 17$)</td>
<td>5.65 (3.35)</td>
<td>3.18 (2.56)</td>
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<tr>
<td>$ls$</td>
<td>Control ($n = 29$)</td>
<td>5.83 (5.86)</td>
<td>6.95 (6.04)</td>
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<tr>
<td></td>
<td>Exercise ($n = 32$)</td>
<td>4.50 (3.57)</td>
<td>2.98 (2.91)</td>
</tr>
<tr>
<td>$ss$</td>
<td>Control ($n = 11$)</td>
<td>5.32 (4.91)</td>
<td>6.20 (5.38)</td>
</tr>
<tr>
<td></td>
<td>Exercise ($n = 16$)</td>
<td>3.69 (3.65)</td>
<td>3.34 (3.35)</td>
</tr>
</tbody>
</table>

### FIGURE 2—Depression scores by exercise group.

![Depression scores by exercise group.](http://www.acsm-msse.org)

### TABLE 3. Changes in depressive symptoms by 5-HTTLPR genotype ($ll/ls$ vs $ss$).

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Group</th>
<th>Pretest BDI</th>
<th>Posttest BDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$ll$</td>
<td>Control ($n = 53$)</td>
<td>5.36 (5.27)</td>
<td>6.51 (5.58)</td>
</tr>
<tr>
<td></td>
<td>Exercise ($n = 49$)</td>
<td>4.90 (3.51)</td>
<td>3.05 (2.77)</td>
</tr>
<tr>
<td>$ss$</td>
<td>Control ($n = 11$)</td>
<td>5.32 (4.91)</td>
<td>6.20 (5.38)</td>
</tr>
<tr>
<td></td>
<td>Exercise ($n = 16$)</td>
<td>3.69 (3.65)</td>
<td>3.34 (3.35)</td>
</tr>
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</table>

### FIGURE 3—Depression scores by 5-HTTLPR genotype within the exercise group.

![Depression scores by 5-HTTLPR genotype within the exercise group.](http://www.acsm-msse.org)
with the effect size (0.66) found within the general population of a previous meta-analysis (36). Furthermore, a significant difference in the effect of the exercise intervention across 5-HTTLPR genotypes was observed, by which individuals with at least one l allele showed significant decreases in depression scores after the exercise intervention compared with the ss homozygotes.

The effect of exercise on depressive symptoms across 5-HTTLPR genotypes is similar to the effect of SSRI, in which the ss genotype has been associated with a blunted response (39). The results of the current study, along with previous research, suggest that one potential interpretation of this finding is that the physiological mechanisms responsible for decreases in depression scores after the exercise intervention compared with the ss homozygotes.

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5-HT is decreased after SSRI treatment (10,14,18,28,29) and an exercise intervention (47). Furthermore, both exercise (44) and SSRI (27) have been associated with decreases 5-HTT receptors. In addition to these findings in humans, animal models further suggest similar actions of exercise and SSRI on the serotonergic system. Chronic wheel running in mice results in decreased levels of 5-HT mRNA in the dorsal and medial raphe nuclei and a decrease in dorsal raphe nuclei 5-HT mRNA (12). Similarly, SSRI treatment is associated with a decrease in raphe 5-HT mRNA (20,23,45) and 5-HT mRNA in the dorsal raphe nuclei (2,32).

Zanardi et al. (50) and Smeraldi et al. (42) have hypothesized that the blunted response to SSRI observed in the ss genotype may be due to the decreased 5-HTT expression associated with the s allele. A decrease in 5-HTT expression would lead to an increase in extracellular 5-HT, triggering self-inhibition of the 5-HT 1A receptors. A similar self-inhibitory action may occur after exercise. Animal models have demonstrated an increase in 5-HT release after exercise (15). In individuals with the s allele, this increased release of 5-HT may result in a level of extracellular 5-HT that triggers self-inhibition of 5-HT 1A receptors.

However, these results should be interpreted with caution considering the limitations of the present study. First, the sample size needed to detect genetic influence is often quite large. Although the sample size of the current study was sufficient to detect a significant difference across genotype groups, future studies must carefully consider sample size. Second, because of differences in genotype distribution across treatment groups, the ll and the ls genotypes were collapsed into one group for the analysis. Ideally, the analysis would be conducted using all three genotype groups leading to a better understanding of the effect of 5-HTTLPR genotype on response to exercise. In addition, care should be taken in drawing conclusions from the data on the basis of the comparatively low depression scores observed in the ss genotype in both the treatment and the control groups. Although the pretest BDI scores were not significantly different across genotypes, the relatively low depression scores in the ss genotype may result in a floor effect when examining the effect of treatment. Future research should examine the effect of exercise across 5-HTTLPR genotypes in participants with higher levels of depressive symptoms to avoid the potential influence of a floor effect. Furthermore, there is a need for research that aims to better understand the cellular mechanisms underlying the influence of 5-HTTLPR genotype on the antidepressant effects of exercise. Finally, in previous studies, attempts have been made to control for social interaction as a result of the exercise intervention (24,26,40). Although no such attempts were made in this study, the fact that posttest scores for social support were not significantly different from the pretest scores suggests that the decrease in depressive symptoms seen in the exercise group was not the result of social interaction.

Despite these limitations, the significant results of this study suggest the need for future research in the area that may result in significant implications for the treatment of depression. If the difference in response to exercise treatment across 5-HTTLPR genotypes can be replicated within a clinical population, it would support the conclusion that the mechanisms responsible for the exercise-induced alleviation of depressive symptoms are the same mechanisms responsible for decreases in depressive symptoms seen with SSRI treatment. This finding would strengthen the argument that exercise is a legitimate treatment for depressive disorders. Also, this finding would suggest that 5-HTTLPR genotype should be a factor in determining the proper line of treatment for depression, with ll and ls genotype individuals receiving exercise or antidepressant medications, whereas ss individuals would be less likely to benefit from these treatments and may be better served through psychotherapy or other alternative treatments.

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REFERENCES


