

The effects of acute exercise on memory and brain-derived neurotrophic factor (BDNF)

By: [Jennifer L. Etnier](#), [Laurie Wideman](#), [Jeffrey D. Labban](#), Aaron T. Piepmeier, Daniel M. Pendleton, Kelly K. Dvorak, and Katie Becofsky

Etnier JL, Wideman L, Labban JD, Piepmeier A, Pendleton DM, Dvorak K, and Becofsky K. 2016. The effects of acute exercise on memory and brain-derived neurotrophic factor (BDNF). *Journal of Sports and Exercise Psychology*: 38(4): 331-340. PubMed PMID: 27385735

Accepted author manuscript version reprinted, by permission, from *Journal of Sports and Exercise Psychology*, 2016, 38 (4): 331-340, <https://doi.org/10.1123/jsep.2015-0335>. ©Human Kinetics, Inc.

Abstract:

Acute exercise benefits cognition, and some evidence suggests that brain-derived neurotrophic factor (BDNF) plays a role in this effect. The purpose of this study was to explore the dose–response relationship between exercise intensity, memory, and BDNF. Young adults completed 3 exercise sessions at different intensities relative to ventilator threshold (V_t) (VO_{2max} , $V_t - 20\%$, $V_t + 20\%$). For each session, participants exercised for approximately 30 min. Following exercise, they performed the Rey Auditory Verbal Learning Test (RAVLT) to assess short-term memory, learning, and long-term memory recall. Twenty-four hours later, they completed the RAVLT recognition trial, which provided another measure of long-term memory. Blood was drawn before exercise, immediately postexercise, and after the 30-min recall test. Results indicated that long-term memory as assessed after the 24-hr delay differed as a function of exercise intensity with the largest benefits observed following maximal intensity exercise. BDNF data showed a significant increase in response to exercise; however, there were no differences relative to exercise intensity and there were no significant associations between BDNF and memory. Future research is warranted so that we can better understand how to use exercise to benefit cognitive performance.

Keywords: physical activity | cognitive performance | learning | cognition

Article:

Numerous studies have been conducted to explore the potential beneficial effects of a single session of exercise on cognitive performance. This literature has been meta-analytically summarized in three reviews. Chang, Labban, Gapin, and Etnier (2012) reported small beneficial effects when the cognitive task was performed immediately following exercise (Cohen's $d = 0.11$) or after a delay following exercise (Cohen's $d = 0.10$). Lambourne and Tomporowski (2010) restricted their review to studies using aerobic exercise, employing a repeated-measures design, and testing the effects in healthy adults and reported a slightly larger overall effect size (Cohen's $d = 0.20$). When the literature was limited to studies that used memory as the measure of cognitive performance, Roig, Nordbrandt, Geertsens, and Nielsen (2013) reported that a single session of cardiovascular exercise does not significantly benefit short-term memory (standardized mean difference [SMD] = 0.11) but does have a moderate-to-large effect on long-

term memory (SMD = 0.52). As a result of the consistently reported positive effects of acute exercise on cognitive performance, recent research has begun to focus on understanding potential mechanisms underlying this beneficial effect. One mechanism of interest is brain-derived neurotrophic factor (BDNF).

BDNF is of particular interest in understanding the effects of acute exercise on cognitive performance for a number of reasons. First, BDNF is thought to play a key role in the health of the central nervous system because of its impact on neuronal survival, growth, and maintenance (Cotman & Engesser-Cesar, 2002). Second, BDNF has been implicated in the consolidation of memory both in nonhuman animal studies (Johnston & Rose, 2001; Mu, Li, Yao, & Zhou, 1999; Tang et al., 1998) and in human studies (Egan et al., 2003; Hariri et al., 2003). Third, a review of the literature has concluded that a single session of exercise can increase BDNF measured in the periphery (Knaepen, Goekint, Heyman, & Meeusen, 2010). Finally, there is evidence that BDNF crosses the blood–brain barrier (Pan, Banks, Fasold, Bluth, & Kastin, 1998; Poduslo & Curran, 1996) and that measures of BDNF in the central nervous system (cBDNF) correlate with measures of BDNF from the periphery (pBDNF) (Rasmussen et al., 2009; Seifert et al., 2010). However, it is important to point out that these latter findings are equivocal—some authors have argued that BDNF does not cross the blood–brain barrier (Pardridge, 2007; Pardridge, Wu, & Sakane, 1998), and results from one study do not support a link between pBDNF and cBDNF (Kyeremanteng, James, Mackay, & Merali, 2012). Despite the evidence supporting the potential role of BDNF in explaining the effects of exercise on cognitive performance, thus far very few studies with humans have examined the effects of acute exercise on BDNF relative to the behavioral effects observed on cognitive measures (Ferris, Williams, & Shen, 2007; Griffin et al., 2011; Lee et al., 2014; Skriver et al., 2014; Tonoli et al., 2015; Tsai et al., 2014; Winter et al., 2007).

In reviewing the literature on acute exercise, pBDNF, and cognitive performance, there are several evident commonalities. In all of these studies, BDNF was assessed from serum (Ferris et al., 2007; Griffin et al., 2011; Lee et al., 2014; Skriver et al., 2014; Tonoli et al., 2015; Tsai et al., 2014; Winter et al., 2007) or plasma (Skriver et al., 2014) and hence provides a measure of pBDNF (henceforth referred to as BDNF). In response to acute exercise, all of the studies demonstrated improvements in measures of cognitive performance, and all of the studies that used serum measures demonstrated increases in BDNF. There is a lack of consistency, however, with regard to reports of significant associations between changes in BDNF and changes in cognitive performance. Winter et al., Lee et al., and Skriver et al. reported positive associations between BDNF and cognitive performance; Ferris et al. and Tsai et al. observed nonsignificant relationships; and Griffin et al. and Tonoli et al. did not test the relationship. Importantly, in all of the studies demonstrating a positive relationship, cognitive performance was assessed using memory tasks including measures of relational memory (Winter et al., 2007), working memory (Lee et al., 2014), and motor memory (Skriver et al., 2014). By contrast, in the two studies in which an association between BDNF and cognition was not found, the cognitive measure was not a measure of memory. In these studies, the cognitive measures used were measures of attention (Tsai et al., 2014), information processing (Ferris et al., 2007), and executive function (Ferris et al., 2007). Given that the extant literature supporting the role of BDNF in cognitive performance has focused on measures of memory and learning (Egan et al., 2003; Hariri et al.,

2003), the choice of cognitive measures in Ferris et al. and Tsai et al. may have limited their ability to observe relationships.

In looking more closely at the studies demonstrating relationships between BDNF and memory, there is only one study in which a dose–response relationship between exercise intensity and memory was tested. Winter et al. (2007) used a within-subjects design to compare the effects of 15 min of quiet rest, 40 min of low-intensity (aerobic) running, and 6 min of high-intensity (anaerobic) running before a visual paired associate learning session that consisted of five blocks of trials followed by retention measures at 1 hr, 24 hr, and 7 days. Results for learning showed that the high-intensity condition resulted in quicker learning of the paired associations and better long-term memory after 1 week than in either of the other conditions. Results also showed that those who had more sustained elevations of BDNF (change from postexercise to postlearning) following the high-intensity exercise also had better immediate learning. The results of this study show that high-intensity exercise benefits memory, but they do not provide a robust test of the dose–response relationship between exercise intensity and memory. This is because while the exercise conditions differed in terms of intensity, they also differed dramatically in terms of the duration of the exercise (40 min vs. 6 min) and the energy source required for exercise (aerobic vs. anaerobic). This makes it difficult to understand how intensity per se is related to either the behavioral or the physiological responses to the exercise.

Thus, the primary purpose of this study is to extend the previous research by exploring dose–response relationships between exercise intensity and memory and by testing associations with exercise-induced changes in BDNF. The design that was adopted for this study was based upon Ferris et al. (2007), who measured BDNF and cognitive performance in response to a maximal graded exercise test (GXT), a ventilatory threshold (V_t) + 10% condition, and a V_t – 20% condition. Although they did not assess memory, they provided evidence of a dose–response relationship between exercise intensity and BDNF with BDNF increasing by 30% in the GXT condition, by 13% in the V_t + 10% condition, and by 10% in the V_t – 20% condition. Because of our interest in understanding how BDNF might explain cognitive benefits of acute exercise, we hoped to achieve similar changes in BDNF by using (and slightly adapting) these same exercise intensities. Thus, we also included a maximal exercise condition and a V_t – 20% condition, and then, to attempt to obtain a larger spread between the levels of BDNF observed, we included a V_t + 20% condition. Based upon the findings of Winter et al. (2007) and the expected BDNF effects observed by Ferris et al., it was hypothesized that BDNF would increase more and that memory would benefit more from maximal intensity aerobic exercise than from either other intensity of aerobic exercise.

A second purpose of the study was to examine how dose–response relationships between exercise intensity and memory performance might be further distinguished by determining whether the effects are evident for short-term memory, learning, or long-term memory. It was expected that results would differ depending upon the particular type of memory examined. In particular, based upon the findings of Winter et al. (2007), we anticipated that intensity-dependent effects would be most evidence for measures of long-term memory. Given that BDNF has been implicated as important for both short- and long-term hippocampal-dependent memory (Lu, Christian, & Lu, 2008), this is an important direction for research.

Methods

Participants

Sixteen young ($M = 23.06$ years, $SD = 2.18$) adult men ($n = 9$) and women ($n = 7$) participated in the study. Female participants were tested during the early follicular phase of their menstrual cycle, and estradiol was assessed to ensure that there were not differences across testing days. Participants were instructed to drink 1 L of water the night before each session, not to eat or drink anything except water after midnight and before testing, to abstain from smoking in the 3 hr before testing, and to abstain from exercise before testing.

Memory Task

The Rey Auditory Verbal Learning Test (RAVLT) measures episodic memory and was used to assess learning, short-term memory, and long-term memory (Schmidt, 1996). There are several versions of the RAVLT, and for this study we selected three versions that have been shown to be equally difficult in a sample of college students (Schmidt, 1996). The use of alternate forms of the RAVLT is especially important in a repeated-measures design to reduce any practice effects that may bias the results. In particular, the word lists used were from Lezak (1983); Crawford, Stewart, and Moore (1989); and Majdan, Sziklas, and Jones-Gotman (1996). The particular word list used during a given session was selected at random. For each session, participants were read a primary word list (List A) consisting of 15 words. After hearing List A, participants were asked to recall as many words as they could remember in any order. List A was repeated a total of five times (Trials 1–5), and participants were asked to recall the words following each trial. Performance on Trial 1 is considered to be indicative of short-term memory. The change in performance across Trials 1–5 provided a measure of learning (Lezak, Howieson, & Loring, 2004). After the fifth trial, participants heard a new list of 15 words (List B) and were asked to recall as many of these new words from List B as possible (Trial B). Then, without hearing the list again, they were asked to recall as many words from List A as they could remember (Trial 6). Following Trial 6, participants were asked to sit quietly or to read until 30 min following exercise. At this time, participants were asked to again recall as many words as possible from List A (30-min recall).

The next day (approximately 24 hr later), participants were contacted by telephone to complete the 24-hr recognition test. They were read a list consisting of the words from List A, the words from List B, and 20 distractor words that were on neither original list presented in a mixed order. They were asked to verbally identify whether each word had been on List A, List B, or neither list. Performance at the 24-hr recognition test was operationalized as the total number of words correctly identified as having been heard before (24-hr recognition) and the number of words correctly attributed as being from List A or List B (24-hr attributions). These provided additional measures of long-term memory.

Maximal Graded Exercise Test

Participants completed a horizontal running protocol on a treadmill to assess VO_{2max} and V_t . The horizontal running protocol was used to be most similar to the other two exercise sessions in

terms of the grade of the treadmill (0% grade) and the duration of the test. Using horizontal running protocols, participants typically reach maximal voluntary exertion after approximately 30 min, which was the duration used for the other two exercise sessions. Participants were fitted with a face mask that covered their nose and mouth and that allowed for the capture of exhaled air by the metabolic cart (Vmax 229LV LITE, SensorMedics, Yorba Linda, CA). They then performed one of two horizontal running protocols dependent upon their estimated fitness, which was judged based upon their responses to the National Health and Nutrition Examination Survey. This was done so that the duration of the exercise would be approximately 30 min. Participants who were expected to have low to normal fitness levels ran the horizontal running protocol 60, which begins at 3.54 kph. Participants who were expected to have higher fitness levels ran the horizontal running protocol 120, which skips the first six stages used in the other protocol and begins at 7.24 kph. In both protocols, the speed of the treadmill was increased by 0.64 kph every 2 min. Maximal volitional exhaustion was identified when participants reached two of three criteria (respiratory exchange ratio > 1.1 , plateau in VO_2 , rating of perceived exertion [RPE] > 17) established by the American College of Sports Medicine (2014). As soon as the participant reached maximal volitional exhaustion, the speed of the treadmill was lowered to 3.22 kph for a cooldown that lasted no longer than 3 min. V_t was identified from the GXT data using the automated software available on the Vmax system. The Vmax system uses dual criteria of V_e/VO_2 (ventilation relative to oxygen consumption) and $V_e/V\text{CO}_2$ (ventilation relative to carbon dioxide) to identify V_t . Once V_t was identified, the treadmill speeds associated with $V_t - 20\%$ and $V_t + 20\%$ were then established. Approximately 35 min after completing the maximal test (after the memory task had been completed), participants were asked to put the face mask back on and to exercise for 3–5 min more on the treadmill. During this time, researchers used the treadmill speed associated with the $V_t - 20\%$ and confirmed that the selected speed would produce the proper heart rate and VO_2 response. If the speed did not produce the correct heart rate and VO_2 response, minor adjustments in speed were made until the correct heart rate and VO_2 associated with $V_t - 20\%$ were reached. Next, the same steps were followed for $V_t + 20\%$ to confirm the proper speed selection.

Submaximal Exercise Sessions

Both of the submaximal sessions included a 3-min warm-up followed by 27 min of exercise at the prescribed exercise intensity (for a total exercise time of 30 min). Following this, the treadmill speed was reduced and participants were allowed to continue running or walking on the treadmill for not longer than 3 min as a cooldown.

Blood Draws, Handling, and Assays

Blood samples were taken using venipuncture from the antecubital vein at three time points. These time points were before exercise (pre-exercise), immediately after exercise (postexercise), and immediately after 30-minute recall (post-memory test). Two 7 mL samples were collected in serum tubes at each time point so that duplicate assays could be conducted. The blood samples were handled and assayed in accord with the procedures published by Quantikine (<http://www.rndsystems.com/pdf/DBD00.pdf>) for the assessment of BDNF. Pre-exercise samples from the female participants were also assayed using an enzyme-linked immunosorbent assay (ELISA) from ALPCO (Salem, NH) to assess total estradiol.

Procedures

A repeated-measures design was used in this study. Participants came to the laboratory for three testing sessions (see Table 1). Sessions were at least 48 hr apart, began between 6 and 9 a.m. and, for a given participant, started at essentially the same time of day (within a 1-hr period). On the first day, participants were asked to read and sign a written informed consent approved by the university's Institutional Review Board. In the first session, all participants performed the maximal graded exercise test so that the effects of maximal intensity exercise on cognition could be observed and to provide an assessment of V_t to be used in the subsequent sessions. In sessions 2 and 3, participants performed a submaximal exercise session for 30 min at one of two randomly selected exercise intensities ($V_t - 20\%$, $V_t + 20\%$).

Table 1. Procedures Followed for Sessions 1–3

| Session 1 (VO_{2max}) | Session 2 | Session 3 |
|-------------------------------|---|---|
| Consent and info | | |
| Blood draw (pre-exercise) | Blood draw (pre-exercise) | Blood draw (pre-exercise) |
| Exercise (VO_{2max}) | Exercise ($V_t + 20\%$ or $V_t - 20\%$) | Exercise ($V_t + 20\%$ or $V_t - 20\%$) |
| Blood draw (postexercise) | Blood draw (postexercise) | Blood draw (postexercise) |
| RAVLT (Trials 1–7) | RAVLT (Trials 1–7) | RAVLT (Trials 1–7) |
| RAVLT 30-min recall | RAVLT 30-min recall | RAVLT 30-min recall |
| Blood draw (post-memory test) | Blood draw (post-memory test) | Blood draw (post-memory test) |
| Confirmation of VT | | |
| 24-hr recognition | 24-hr recognition | 24-hr recognition |

Note. RAVLT = Rey Auditory Verbal Learning Test; V_t = ventilatory threshold.

For all testing days, participants were fitted with a heart rate monitor and asked to sit quietly for 5 min. Following this rest period, resting heart rate was recorded (resting HR). Participants then had their blood drawn (pre-exercise) and moved to the treadmill. Next, they exercised at their assigned exercise intensity level for that day. Measures of HR and RPE using the Borg 6–20 scale (Borg, 1982) were assessed every 3 min throughout the exercise session. Following exercise, blood was drawn (postexercise) and participants were asked to perform Trials 1–5, Trial B, and Trial 6 of the memory task. For the next 30 min, participants were allowed to read on their own. Immediately following this, they were asked to perform Trial 7 (the recall trial of the memory test) and then blood was drawn again (post-memory test). The following day (approximately 24 hr later), participants were called at a scheduled time and were asked to perform the recognition trial.

Statistical Analyses

To ensure that baseline levels of BDNF and estradiol (women only) were equivalent across testing sessions, one-way repeated-measures analyses of variance (RM ANOVAs) were conducted as a function of exercise intensity ($V_t - 20\%$, $V_t + 20\%$, VO_{2max}). As a manipulation check, RM ANOVAs were used to examine exercise performance (work, maximum heart rate, and average RPE) as a function of exercise intensity. In addition, a single-sample *t* test was used to compare the duration of the exercise in the VO_{2max} condition with 30 min (the amount of time established a priori for the $V_t - 20\%$ and $V_t + 20\%$ conditions).

Performance on the memory test was analyzed for short-term memory (Trial 1), learning (performance on Trials 1–5), and long-term memory (30-min delay, 24-hr recognition, 24-hr attributions). Trial 1, 30-min delay, and 24-hr attributions were analyzed using separate RM ANOVAs with exercise intensity as the within-subject independent variable. Performance across Trials 1–5 was assessed using a 3×5 RM ANOVA to assess the effects of exercise intensity and trials (1–5) on performance.

BDNF was examined using a 3×3 RM ANOVA to analyze exercise intensity and time (pre-exercise, postexercise, post-memory test) effects. Relationships between BDNF and memory were examined within each exercise intensity level (as performed by Winter et al., 2007) with alpha adjusted by the number of correlations conducted ($\alpha = .05/16 = .003$). The BDNF variables that were used were the postexercise level, the postrecall level, the change from pre-exercise to postexercise expressed as percent gain, and the maintenance of BDNF defined as (postrecall – postexercise)/postexercise. The memory variables included in the correlation analyses were Trial 1, 30-min delay, 24-hr recognition, and 24-hr attributions.

For all RM ANOVAs, the sphericity assumption was examined when appropriate, and if necessary a Huynh–Feldt adjustment was made to the degrees of freedom. Partial eta-squared (η^2_{partial}) is presented as a measure of effect size. Following observation of significant effects, Bonferroni post hoc pairwise comparisons were conducted.

Results

Descriptive information regarding the sample is provided in Table 2.

Table 2. Descriptive Information for the Sample

| Variable | Range | <i>M</i> | <i>SD</i> |
|--------------------------------|-------------|----------|-----------|
| Age | 19–27 | 23.06 | 2.18 |
| VO _{2max} (ml/kg/min) | 33.70–50.40 | 42.70 | 5.51 |
| BMI | 18.54–31.93 | 24.30 | 4.01 |

Note. BMI = body mass index.

Baseline Levels

There were no significant differences in estradiol, $F(2, 8) = 0.25, p > .05, \eta^2_{\text{partial}} = .06$, or BDNF, $F(2, 28) = 0.03, p > .05, \eta^2_{\text{partial}} = .002$, at baseline between any of the testing sessions.

Exercise Performance

Descriptive data for work (kilometers completed), maximum heart rate, and RPE are shown in Table 3. There were significant differences in work, $F(2, 28) = 15.92, p < .001, \eta^2_{\text{partial}} = 0.53$; maximum heart rate, $F(2, 28) = 92.40, p < .001, \eta^2_{\text{partial}} = 0.87$; and average RPE, $F(1.27, 17.79) = 11.17, p < .01, \eta^2_{\text{partial}} = 0.44$ as a function of exercise intensity. As expected, the maximum heart rate observed during exercise was significantly higher for the VO_{2max} condition as compared with the Vt + 20% condition, which was significantly higher than the Vt – 20% condition. Also as expected, the amount of work completed was significantly higher for the Vt + 20% condition as compared with the VO_{2max} condition and the Vt – 20% condition. For RPE, the

average RPE was significantly higher for the $Vt + 20\%$ condition and the VO_{2max} condition as compared with the $Vt - 20\%$ condition. In performing the VO_{2max} test, participants exercised for an average of 29 min ($SD = 6$ min 2 s), which was not significantly different from the 30 min of exercise performed in the other two exercise intensity conditions, $t(15) = -0.67, p > .05$.

Table 3. Work (Kilometers Completed), Maximum Heart Rate, and Average RPE During Each Exercise Condition

| Variable | Range | <i>M</i> | <i>SD</i> |
|-----------------------|------------|----------|-----------|
| VO_{2max} condition | | | |
| Work (km) | 1.62–5.78 | 4.29 | 1.12 |
| Maximum HR (bpm) | 173–205 | 193.69 | 8.60 |
| RPE | 3.88–15.40 | 12.52 | 2.76 |
| $Vt - 20\%$ condition | | | |
| Work (km) | 2.95–4.55 | 3.78 | 0.47 |
| Maximum HR | 135–191 | 154.93 | 14.61 |
| RPE | 7.00–14.00 | 10.66 | 2.20 |
| $Vt + 20\%$ condition | | | |
| Work (km) | 3.37–6.41 | 4.86 | 0.76 |
| Maximum HR | 171–204 | 185.00 | 7.96 |
| RPE | 8.40–16.40 | 13.97 | 2.16 |

Note. RPE = the average rating of perceived exertion reports across the exercise condition; work = kilometers completed; maximum HR = the maximum heart rate observed during the exercise condition; Vt = ventilatory threshold.

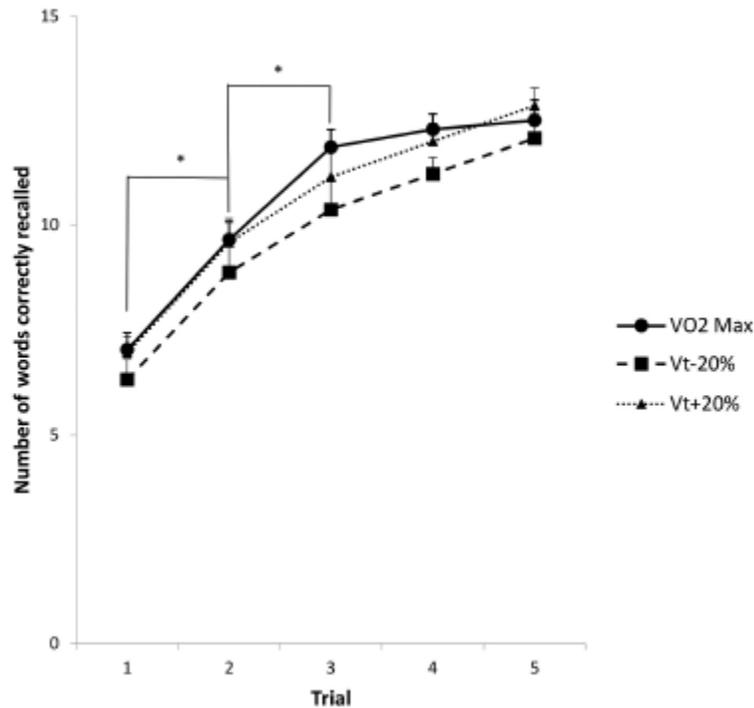


Figure 1. Average number of words (with standard error) correctly recalled at Trials 1–5 as a function of exercise intensity.

Memory Performance

Short-Term Memory. Results for short-term memory indicated that there was not a significant difference in Trial 1 performance as a function of exercise intensity, $F(2, 28) = 0.85, p = .44, \eta^2_{\text{partial}} = 0.06$.

Learning. Results for Trials 1–5 indicated that there was a nearly significant difference in performance as a function of exercise intensity, $F(2, 26) = 3.30, p = .05, \eta^2_{\text{partial}} = 0.20$, and there was a significant difference as a function of trials, $F(4, 52) = 121.02, p < .001, \eta^2_{\text{partial}} = 0.90$. The main effect for trials indicated that performance on the memory task improved significantly from Trial 1 ($M = 6.74, SE = 0.29$) to Trial 2 ($M = 9.36, SE = 0.41$) to Trial 3 ($M = 11.12, SE = 0.48$) and then plateaued, such that performance at Trial 3 was not significantly different from Trial 4 ($M = 11.83, SE = 0.28$), and Trial 4 was not significantly different from Trial 5 ($M = 12.48, SE = 0.38$). The interaction of Exercise Intensity \times Trial was not significant, $F(8, 104) = 0.45, p = .89, \eta^2_{\text{partial}} = 0.03$. (See Figure 1.)

Long-Term Memory. Performance at the 30-min delay did not differ significantly as a function of exercise intensity, $F(2, 28) = 1.80, p > .05, \eta^2_{\text{partial}} = 0.11$.

There was a significant difference in 24-hr recognition as a function of exercise intensity, $F(2, 28) = 4.25, p = .02, \eta^2_{\text{partial}} = 0.23$, such that performance was significantly better after the $VO_{2\text{max}}$ day ($M = 22.33, SE = 0.63$) as compared with the $Vt - 20\%$ day ($M = 19.93, SE = 0.80$). Performance on the $Vt + 20\%$ day was not significantly different from either of the other exercise intensity conditions ($M = 20.47, SE = 0.90$). (See Figure 2.)

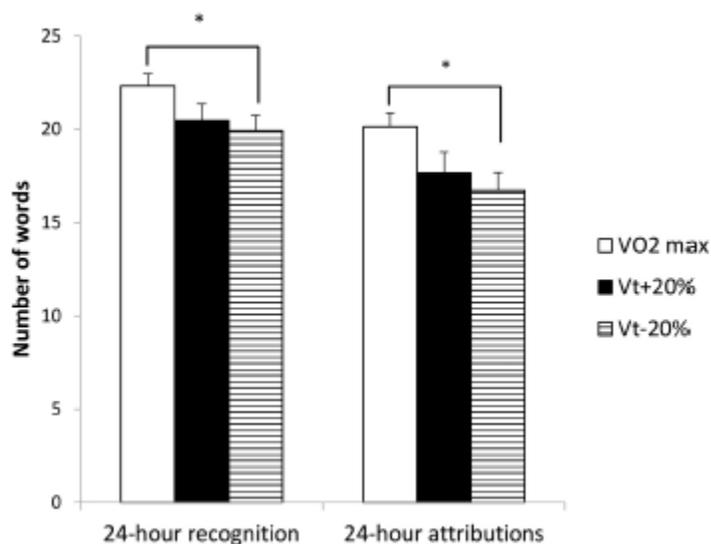


Figure 2. Averages for 24-hr long-term memory measures (with standard error) as a function of exercise intensity.

Similarly, 24-hr attributions were significantly different as a function of exercise intensity, $F(2, 28) = 5.78, p = .008, \eta^2_{\text{partial}} = 0.29$, with means indicating that performance was significantly better after the $VO_{2\text{max}}$ condition ($M = 20.13, SE = 0.74$) as compared with the $Vt - 20\%$ condition ($M = 16.73, SE = 0.96$). Performance after the $Vt + 20\%$ condition was not

significantly different from either of the other exercise intensity conditions ($M = 17.67$, $SE = 1.12$). (See Figure 2.)

BDNF

Results for the BDNF data indicated that there was a significant main effect for time, $F(2, 26) = 11.16$, $p < .001$, $\eta^2_{\text{partial}} = 0.46$, but the main effect for exercise intensity, $F(2, 26) = 0.95$, $p > .05$, $\eta^2_{\text{partial}} = 0.07$, and the interaction of Exercise Intensity \times Time $F(2.73, 35.43) = 0.92$, $p > .05$, $\eta^2_{\text{partial}} = 0.07$, were not significant (see Figure 3). The main effect for time indicated that serum BDNF increased significantly from baseline ($M = 15438.3 \pm 1577.1$ pg/mL) to postexercise ($M = 21502.93$, $SE = 2117.42$) and then decreased significantly by 30-min postexercise ($M = 17010.20$, $SE = 1074.24$) to a level that was not significantly different from baseline.

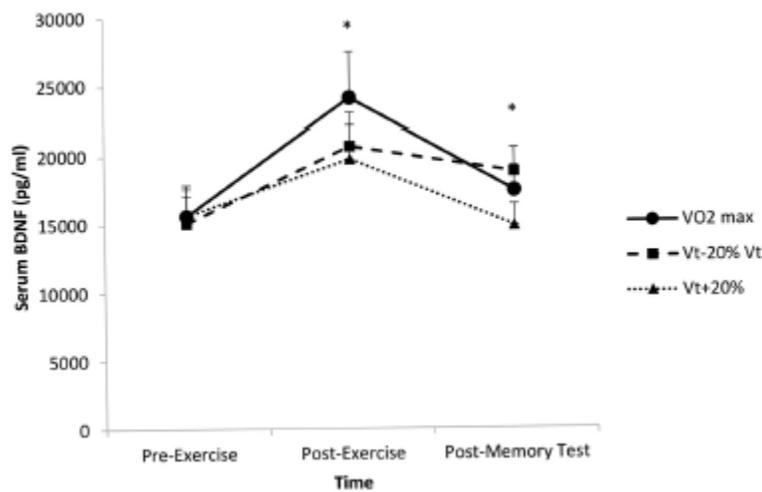


Figure 3. Average serum brain-derived neurotrophic factor (BDNF; with standard error) as a function of time and exercise intensity. *Significant difference between this time point and the previous time point irrespective of exercise intensity.

Correlations Between BDNF and Long-Term Memory

Associations between measures of BDNF and memory were not significant ($p > .003$) for any of the relationships assessed from data obtained during the $VO_{2\text{max}}$, the $Vt + 20\%$, or the $Vt - 20\%$ exercise intensity conditions. These findings are available upon request.

Discussion

The primary purpose of this study was to test the dose–response effects of exercise intensity on memory performance and to assess the relationship between BDNF responses to exercise and memory. A secondary goal was to assess how these relationships might differ for learning, short-term memory, and long-term memory. This is an important direction for future research because of our limited understanding of how exercise intensity influences cognitive performance and because of the importance of identifying underlying mechanisms of the effects of exercise on memory.

Results indicated that there was no significant difference in short-term memory as a function of condition. Thus, the various intensities of exercise did not differentially influence how many words participants were able to recall following the first exposure to the word list. This particular memory measure was not reported in Winter et al. (2007) or in Skriver et al. (2014), so a direct comparison between these studies is not possible. Based upon the results of a previous meta-analysis (Roig et al., 2013), we anticipated that exercise would have a small positive effect on short-term memory; however, because a no-treatment control group was not used, we are not able to draw conclusions from these results as to whether acute exercise influenced short-term memory. That is, while we expected that exercise would benefit memory, because a no-treatment control group was not used, we do not know if participants performed better than, the same as, or worse than a no-treatment control would have performed. That being said, the results from the current study certainly suggest that acute exercise does not influence short-term memory in an intensity-dependent way, at least as a function of the exercise intensities included in this study. Evidence from a meta-analytic review (Chang et al., 2012) indicates that there is an association between exercise intensity and cognitive performance assessed after exercise that is moderated by the timing of the cognitive tests. In particular, exercise at lower intensities has been shown to be most beneficial for cognitive performance assessed immediately after exercise while exercise at higher intensities is better for cognitive performance assessed after a delay following exercise. Given these meta-analytic results, it seems possible that the lowest intensity exercise condition in this study (Vt – 20%) was not a low enough intensity to benefit short-term memory. Hence, future research will be needed to determine if short-term memory is sensitive to intensity effects when a broader range of intensities is used.

There was a significant difference in learning of the word list across exposures (Trials 1–5) such that participants remembered increasingly more words after each exposure until Trial 3 at which point they maintained their ability to remember words across Trials 4 and 5. The difference in learning as a function of exercise intensity was nearly significant. Given the limited research exploring the dose–response effects of exercise intensity on memory performance and the well-known arguments against the sanctity of $\alpha = .05$ (Rosnow & Rosenthal, 1989; Trafimow, 2014), we believe that consideration of this nearly significant effect is warranted. Hence, we conducted additional two-way RM ANOVAs to compare performance on Trials 1–5 of the RAVLT between the VO_{2max} day and the Vt – 20% day and to compare between the Vt + 20% day and the Vt – 20% day. Results of these analyses indicated that there was a significant effect for condition for the first comparison indicating that learning across trials was significantly better on the VO_{2max} day than the Vt – 20% day, $F(1, 13) = 5.75, p < .05$. However, there was no significant difference in learning between the Vt + 20% day and the Vt – 20% day, $F(1, 13) = 3.97, p = .07$. Future study is needed to identify whether this is a reliable effect indicating that learning is best after exercising to maximal voluntary exhaustion. Importantly, the finding in this study that the highest exercise intensity administered resulted in the best memory performance is similar to the findings for learning reported by Winter et al. (2007), who observed that learning speed (the increase in correct responses across trials) was significantly better following the high-intensity exercise session as compared with the low- and moderate-intensity exercise sessions.

Findings for long-term memory (24-hr recognition and 24-hr attributions) indicated that memory performance 24 hr following the exercise session was significantly better as a result of completing the VO_{2max} test as compared with completing the Vt – 20% session. This finding is

also consistent with Winter et al. (2007), who reported that long-term memory was significantly better following the high-intensity exercise session as compared with the moderate-intensity session. In addition, this finding is consistent with the aforementioned meta-analytic finding that higher intensity exercise is most beneficial for cognitive performance when assessed after a delay following exercise.

With regard to the changes in BDNF as a function of exercise, the results of this study support past literature showing that a single session of exercise increases peripheral levels of BDNF as assessed in the serum (Ferris et al., 2007; Griffin et al., 2011; Lee et al., 2014; Lu et al., 2008; Rasmussen et al., 2009; Rojas Vega et al., 2006; Tang, Chu, Hui, Helmeste, & Law, 2008; Tonoli et al., 2015; Tsai et al., 2014; Winter et al., 2007). Interestingly, BDNF did not change in a dose–response fashion with respect to the intensity of the exercise bout. In fact, results indicated that the three conditions resulted in similar relative change in response to the exercise (VO_{2max} : 43% increase; $Vt + 20\%$: 48% increase; $Vt - 20\%$: 37% increase). This finding was unexpected given past evidence of a positive relationship between exercise intensity and BDNF concentrations in serum (Knaepen et al., 2010). This lack of significant change in serum BDNF despite seeing an exercise intensity effect for learning and long-term memory may explain why there were no significant correlations between BDNF measures and memory measures. This failure to observe an association between BDNF and memory can be interpreted in a number of ways. First, it is possible that BDNF is not the mechanism by which acute exercise affects memory performance. However, this may be an overstatement given some of the limitations inherent in this study. In particular, one limitation is that we only assessed BDNF in the periphery, and it is possible that changes in BDNF observed in this study are not related closely enough to the changes that occur centrally for this association to reach significance. In other words, the measures of BDNF assessed in the periphery may not correlate tightly enough with measures of central BDNF to provide a fair indication of the extent to which BDNF influences exercise-induced memory benefits. A second limitation is that we used a commercially available ELISA kit that primarily assesses the mature isoform of BDNF, and it is possible that mature BDNF may not provide the best evidence with regard to this research question. Piepmeier and Etnier (2015) have argued that future studies would benefit from specifically exploring two of the BDNF isoforms (pro, mature) that serve contrasting roles with regard to cellular activation during memory tasks. Despite the limitations inherent in this study, given the previously described rationale for exploring BDNF as a mechanism of the effects of exercise on memory and the promising evidence from animal studies, we believe that future research should continue to explore BDNF.

Before discussing the implications of this study, it is important to acknowledge the delimitations of this study. We refer to these as “delimitations” because these were recognized shortcomings that we accepted a priori as we considered participant burden (3 testing days, repeated blood draws) relative to the addition of more testing sessions (i.e., a nonexercise day, a second VO_{2max} session on a randomly assigned day). First, although the duration of the exercise on the VO_{2max} day was not significantly different from the exercise duration on the $Vt + 20\%$ and the $Vt - 20\%$ days, there was variability in the duration of this session across participants ($SD = 6 \text{ min } 2 \text{ s}$), which might then have made the effects on memory more variable. We created a scenario such that the VO_{2max} test would take approximately 30 min to complete (by using a “flat” protocol and by individualizing the initial starting speed based upon self-reported physical activity levels).

However, this shortcoming could not be completely eradicated because every individual reached his or her maximal capacity at slightly different times.

A second limitation of the study is that although the $V_t + 20\%$ and the $V_t - 20\%$ conditions were performed in a randomized order, the VO_{2max} condition was performed by all participants on the first day of the study (so that V_t could be identified). This limitation was partially addressed by randomly assigning equivalent word lists to the various conditions. However, it is possible that performance on the VO_{2max} day was impacted by this also being the first day of participation in the study. That being said, this explanation would likely have resulted in performance on that day being *worse* than it would have been at subsequent sessions (performance was likely to improve because of familiarity with the testing scenario). Given that performance was actually the best on the VO_{2max} day, the limitation of performing the VO_{2max} day first is not itself a likely explanation of the results. Third, because the primary purpose of the study was to compare exercise of various intensities, a no-treatment control condition was not included; thus comparisons in performance can only be made relative to exercise intensity. Although a meta-analytic review of the literature on memory (Roig et al., 2013) showed that acute exercise has a small effect on short-term memory and a larger effect on long-term memory, additional research is warranted to further our understanding of the extent to which acute exercise influences short-term memory as compared with no treatment and as a function of exercise intensity.

Lastly, it is intriguing to think about the differences in the effects that were observed in this study relative to the notion of workload. In our study design, we equated the duration of the exercise and manipulated intensity level. However, it is important to note that although participants in the VO_{2max} condition exercised to volitional exhaustion and presumably reached the highest intensity of exercise that they were capable of after approximately 30 min of exercise, they were not exercising at maximal intensity for the entire session. In fact, they built up to this level of intensity gradually so that the actual total amount of work completed and the average perceived effort during the various exercise conditions was greatest for the $V_t + 20\%$ session followed by the VO_{2max} session and then the $V_t - 20\%$ condition. Although not significant, the changes in BDNF in response to exercise show a similar pattern with the biggest change observed after $V_t + 20\%$ (48%), followed by VO_{2max} (43%), followed by $V_t - 20\%$ (37%). This has us wondering whether it is the high intensity per se that is most important in predicting changes in memory (with the highest intensity, VO_{2max} , being the best) or whether it is the total work completed in a fixed period of time that is most important with a moderate amount's being best (as achieved during the VO_{2max} day).

Given the necessary delimitations of our study, future research focused on the dose–response effects of exercise intensity on memory (and BDNF) would benefit from using a design whereby VO_{2max} is assessed on the first day of testing as a marker of fitness and for the express purpose of assigning future workload. Then participants would be asked to perform additional testing sessions in a randomly presented order to examine dose–response effects. For instance, one could begin to address the question of the effects of intensity and duration while controlling for workload by designing a study that equated exercise sessions on total work completed but achieved this through very different intensity/duration combinations (high intensity, short duration vs. low intensity, long duration). The challenge in this area of research is to understand more clearly the aspect of the acute exercise that is important for predicting the effects on

cognitive performance. At this time, we do not know if intensity, duration, or work is most important for determining the effects on cognition, and, since these variables are inextricably linked to one another, it is challenging to design studies that control for two of these while systematically manipulating the third.

Additional suggestions with regard to future research are related to the assessment of BDNF. One important consideration is that BDNF itself is influenced by learning (Kesslak, So, Choi, Cotman, & Gomez-Pinilla, 1998). Because of this, if we are to better understand the role of BDNF in explaining the effects of exercise on memory, studies must test the effects of exercise and learning in isolation versus the effects of exercise and learning in combination to better understand their unique and synergistic influences on BDNF. A second important consideration is that by focusing on peripheral measures of total BDNF, we clearly are not providing insights as to the actual effects of exercise on cBDNF that are important for learning. As previously mentioned, pBDNF are only indirectly linked to cBDNF, and mature and immature forms of BDNF have different effects in the central nervous system. Further, and importantly, we know that BDNF exerts its influence on long-term potentiation through the effects of mature BDNF on the TrkB signaling cascade (Minichiello, 2009). Clearly, much additional work is needed before we can fully understand precisely how exercise might influence long-term potentiation through BDNF-mediated effects on the TrkB signaling cascade.

In sum, results of this study support a threshold effect of exercise intensity on learning and long-term memory and are consistent with Winter et al. (2007) in suggesting that an acute bout of higher intensity exercise (VO_{2max}) results in significantly better effects than lower intensity exercise ($-20\% Vt$). This is an intriguing finding because of the obvious implications for learning paradigms such as might be seen in school settings. It is possible that participation in high-intensity exercise for 30 min could have benefits in terms of academic performance. At the other end of the aging spectrum, if maximal intensity exercise benefits long-term memory, then perhaps exercise may be used as an intervention to benefit persons suffering from mild cognitive impairment. Although the results of this study do not support a role of serum BDNF in predicting memory performance, we believe future research should continue to explore BDNF and look forward to the day when BDNF can be assessed in the human central nervous system while also encouraging researchers to use assay techniques that allow for a distinction between BDNF isoforms in serum.

Acknowledgments

Funding to support this research was provided by the Safrit Measurement in Research Award from the University of North Carolina at Greensboro.

References

American College of Sports Medicine. (2014). *ACSM's guidelines for exercise testing and prescription* (9th ed.). Baltimore, MD: Wolters Kluwer.

Borg, G.A. (1982). Psychophysical bases of perceived exertion. *Medicine and Science in Sports and Exercise*, 14(5), 377–381. doi:10.1249/00005768-198205000-00012

Chang, Y.K., Labban, J.D., Gapin, J.I., & Etnier, J.L. (2012). The effects of acute exercise on cognitive performance: A meta-analysis. *Brain Research, 1453*, 87–101. doi:10.1016/j.brainres.2012.02.068

Cotman, C.W., & Engesser-Cesar, C. (2002). Exercise enhances and protects brain function. *Exercise and Sport Sciences Reviews, 30*(2), 75–79. doi:10.1097/00003677-200204000-00006

Crawford, J.R., Stewart, L.E., & Moore, J.W. (1989). Demonstration of savings on the AVLT and development of a parallel form. *Journal of Clinical and Experimental Neuropsychology, 11*(6), 975–981. doi:10.1080/01688638908400950

Egan, M.F., Kojima, M., Callicott, J.H., Goldberg, T.E., Kolachana, B.S., Bertolino, A., . . . Weinberger, D.R. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell, 112*(2), 257–269. doi:10.1016/S0092-8674(03)00035-7

Ferris, L.T., Williams, J.S., & Shen, C.L. (2007). The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. *Medicine and Science in Sports and Exercise, 39*(4), 728–734. doi:10.1249/mss.0b013e31802f04c7

Griffin, É.W., Mullally, S., Foley, C., Warmington, S.A., O'Mara, S.M., & Kelly, A.M. (2011). Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiology & Behavior, 104*(5), 934–941. doi:10.1016/j.physbeh.2011.06.005

Hariri, A.R., Goldberg, T.E., Mattay, V.S., Kolachana, B.S., Callicott, J.H., Egan, M.F., & Weinberger, D.R. (2003). Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. *The Journal of Neuroscience, 23*(17), 6690–6694.

Johnston, A.N., & Rose, S.P. (2001). Memory consolidation in day-old chicks requires BDNF but not NGF or NT-3; an antisense study. *Brain Research, 88*(1–2), 26–36. doi:10.1016/S0169-328X(01)00016-X

Kesslak, J.P., So, V., Choi, J., Cotman, C.W., & Gomez-Pinilla, F. (1998). Learning upregulates brain-derived neurotrophic factor messenger ribonucleic acid: A mechanism to facilitate encoding and circuit maintenance? *Behavioral Neuroscience, 112*(4), 1012–1019. doi:10.1037/0735-7044.112.4.1012

Knaepen, K., Goekint, M., Heyman, E.M., & Meeusen, R. (2010). Neuroplasticity—Exercise-induced response of peripheral brain-derived neurotrophic factor: A systematic review of experimental studies in human subjects. *Sports Medicine (Auckland, N.Z.), 40*(9), 765–801. doi:10.2165/11534530-000000000-00000

Kyeremanteng, C., James, J., Mackay, J., & Merali, Z. (2012). A study of brain and serum brain-derived neurotrophic factor protein in Wistar and Wistar-Kyoto rat strains after electroconvulsive stimulus. *Pharmacopsychiatry*, *45*(6), 244–249. doi:10.1055/s-0032-1306278

Lambourne, K., & Tomporowski, P. (2010). The effect of exercise-induced arousal on cognitive task performance: A meta-regression analysis. *Brain Research*, *1341*, 12–24. doi:10.1016/j.brainres.2010.03.091

Lee, J.K., Koh, A.C., Koh, S.X., Liu, G.J., Nio, A.Q., & Fan, P.W. (2014). Neck cooling and cognitive performance following exercise-induced hyperthermia. *European Journal of Applied Physiology*, *114*(2), 375–384. doi:10.1007/s00421-013-2774-9

Lezak, M.D. (1983). *Neuropsychological assessment* (2nd ed.). New York, NY: Oxford University Press.

Lezak, M.D., Howieson, D.B., & Loring, D.W. (2004). *Neuropsychological assessment* (4th ed.). Oxford, UK: Oxford University Press.

Lu, Y., Christian, K., & Lu, B. (2008). BDNF: A key regulator for protein synthesis-dependent LTP and long-term memory? *Neurobiology of Learning and Memory*, *89*(3), 312–323. doi:10.1016/j.nlm.2007.08.018

Majdan, A., Sziklas, V., & Jones-Gotman, M. (1996). Performance of healthy subjects and patients with resection from the anterior temporal lobe on matched tests of verbal and visuo-perceptual learning. *Journal of Clinical and Experimental Neuropsychology*, *18*(3), 416–430. doi:10.1080/01688639608408998

Minichiello, L. (2009). TrkB signalling pathways in LTP and learning. *Nature Reviews Neuroscience*, *10*(12), 850–860. doi:10.1038/nrn2738

Mu, J.S., Li, W.P., Yao, Z.B., & Zhou, X.F. (1999). Deprivation of endogenous brain-derived neurotrophic factor results in impairment of spatial learning and memory in adult rats. *Brain Research*, *835*(2), 259–265. doi:10.1016/S0006-8993(99)01592-9

Pan, W., Banks, W.A., Fasold, M.B., Bluth, J., & Kastin, A.J. (1998). Transport of brain-derived neurotrophic factor across the blood–brain barrier. *Neuropharmacology*, *37*(12), 1553–1561. doi:S0028390898001415

Pardridge, W.M. (2007). Blood–brain barrier delivery. *Drug Discovery Today*, *12*(1-2), 54–61. doi:10.1016/j.drudis.2006.10.013

Pardridge, W.M., Wu, D., & Sakane, T. (1998). Combined use of carboxyl-directed protein pegylation and vector-mediated blood–brain barrier drug delivery system optimizes brain uptake of brain-derived neurotrophic factor following intravenous administration. *Pharmaceutical Research*, *15*(4), 576–582. doi:10.1023/A:1011981927620

Piepmeyer, A.T., & Etnier, J.L. (2015). Brain-derived neurotrophic factor (BDNF) as a potential mechanism of the effects of acute exercise on cognitive performance. *Journal of Sport and Health Science*, 4, 14–23. doi:10.1016/j.jshs.2014.11.001

Poduslo, J.F., & Curran, G.L. (1996). Permeability at the blood–brain and blood-nerve barriers of the neurotrophic factors: NGF, CNTF, NT-3, BDNF. *Molecular Brain Research*, 36(2), 280–286. doi:0169328X9500250V

Rasmussen, P., Brassard, P., Adser, H., Pedersen, M.V., Leick, L., Hart, E., . . . Pilegaard, H. (2009). Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. *Experimental Physiology*, 94(10), 1062–1069. doi:10.1113/expphysiol.2009.048512

Roig, M., Nordbrandt, S., Geertsen, S.S., & Nielsen, J.B. (2013). The effects of cardiovascular exercise on human memory: A review with meta-analysis. *Neuroscience and Biobehavioral Reviews*, 37(8), 1645–1666. doi:10.1016/j.neubiorev.2013.06.012

Rojas Vega, S., Struder, H.K., Vera Wahrmann, B., Schmidt, A., Bloch, W., & Hollmann, W. (2006). Acute BDNF and cortisol response to low intensity exercise and following ramp incremental exercise to exhaustion in humans. *Brain Research*, 1121(1), 59–65. doi:10.1016/j.brainres.2006.08.105

Rosnow, R.L., & Rosenthal, R. (1989). Statistical procedures and the justification of knowledge in psychological science. *American Psychologist*, 44, 1276–1284. doi:10.1037/0003-066X.44.10.1276

Schmidt, M. (1996). *Rey Auditory Verbal Learning Test: A handbook*. Los Angeles, CA: Western Psychological Services.

Seifert, T., Brassard, P., Wissenberg, M., Rasmussen, P., Nordby, P., Stallknecht, B., . . . Secher, N.H. (2010). Endurance training enhances BDNF release from the human brain. *American Journal of Physiology—Regulatory, Integrative and Comparative Physiology*, 298(2), R372–377. doi:10.1152/ajpregu.00525.2009

Skriver, K., Roig, M., Lundbye-Jensen, J., Pingel, J., Helge, J.W., Kiens, B., & Nielsen, J.B. (2014). Acute exercise improves motor memory: Exploring potential biomarkers. *Neurobiology of Learning and Memory*, 116, 46–58. doi:10.1016/j.nlm.2014.08.004

Tang, M.X., Stern, Y., Marder, K., Bell, K., Gurland, B., Lantigua, R., . . . Mayeux, R. (1998). The APOE-epsilon4 allele and the risk of Alzheimer disease among African Americans, Whites, and Hispanics. *Journal of the American Medical Association*, 279(10), 751–755. doi:10.1001/jama.279.10.751

Tang, S.W., Chu, E., Hui, T., Helmeste, D., & Law, C. (2008). Influence of exercise on serum brain-derived neurotrophic factor concentrations in healthy human subjects. *Neuroscience Letters*, 431(1), 62–65. doi:10.1016/j.neulet.2007.11.019

Tonoli, C., Heyman, E., Buyse, L., Roelands, B., Piacentini, M.F., Bailey, S., . . . Meeusen, R. (2015). Neurotrophins and cognitive functions in T1D compared with healthy controls: Effects of a high-intensity exercise. *Applied Physiology, Nutrition, and Metabolism*, *40*(1), 20–27. doi:10.1139/apnm-2014-0098

Trafimow, D. (2014). Editorial. *Basic and Applied Social Psychology*, *36*(1), 1–2. doi:10.1080/01973533.2014.865505

Tsai, C.L., Chen, F.C., Pan, C.Y., Wang, C.H., Huang, T.H., & Chen, T.C. (2014). Impact of acute aerobic exercise and cardiorespiratory fitness on visuospatial attention performance and serum BDNF levels. *Psychoneuroendocrinology*, *41*, 121–131. doi:10.1016/j.psyneuen.2013.12.014

Winter, B., Breitenstein, C., Mooren, F.C., Voelker, K., Fobker, M., Lechtermann, A., . . . Knecht, S. (2007). High impact running improves learning. *Neurobiology of Learning and Memory*, *87*(4), 597–609. doi:10.1016/j.nlm.2006.11.003