The effects of aerobic exercise intensity on memory in older adults

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Aerobic exercise may enhance memory in older adults. However, the optimal intensity and underlying mechanism are unclear. This community-based study examined the effect of aerobic exercise intensity on memory and general cognitive abilities. Brain-derived neurotrophic factor (BDNF) was examined as a potential mechanism. Sixty-four sedentary older adults participated in one of three groups: 1) high-intensity interval training (HIIT); 2) moderate continuous training (MCT); or 3) stretching control (CON). Prior to and following the intervention, high-interference memory was assessed using a Mnemonic Similarity task and executive functions were assessed using Go Nogo and Flanker tasks. HIIT led to the greatest memory performance compared to MCT and CON \(F(2, 55) = 6.04, p = .004\) and greater improvements in memory correlated with greater increases in fitness \(r_s(46) = .27, p = .03\). Exercise intensity seemed to matter less for executive functioning, as positive trends were observed for both HIIT and MCT. No significant differences in BDNF were found between groups. Overall, these results suggest that aerobic exercise may enhance memory in older adults, with the potential for higher intensity exercise to yield the greatest benefit. While our findings suggest that BDNF does not regulate these adaptations, the mechanisms remain to be determined.

**Novelty bullets:**

- High-intensity interval training results in the greatest memory performance in inactive older adults compared to moderate continuous training or stretching
- Improvement in fitness correlates with improvement in memory performance

**Keywords:** Memory; Executive functions; Cognition, Exercise, Physical activity; High-intensity interval training; Aging; BDNF
Introduction

Aging is associated with a progressive decline in memory (Fjell et al. 2014; Scullin and Bliwise 2015) and physical exercise has been identified as a potentially therapeutic treatment to mitigate this decline (Bherer et al. 2013; Zheng et al. 2016). Higher intensity exercise improves memory for younger adults (Bherer et al. 2013; Déry et al. 2013; Heisz et al. 2017; Heisz et al. 2015); however, the optimal exercise intensity to improve memory in older adults is unknown. The present study examined the impact of different aerobic exercise intensities on memory and other cognitive abilities in older adults.

Advancing age is associated with impaired cognitive function due to the atrophy of key brain structures including the hippocampus, prefrontal cortex (Erickson et al. 2011; Fjell et al. 2014) and white matter tracts (Daselaar et al. 2013). High-interference memory is a subtype of memory function that is particularly vulnerable to age-related changes (Stark et al. 2015). This type of memory requires the creation of distinct, non-overlapping representations to keep similar items separate and minimize interference (Yassa and Stark 2011). Prior work suggests that older adults require a greater degree of dissimilarity between inputs to encode them as distinct stimuli, a phenomenon termed “representational rigidity” (Bullock et al. 2018; Stark et al. 2013). Thus, older adults tend to recruit pattern completion processes, such that they have a propensity to reactivate previously encoded representations when presented with highly similar inputs (Yassa and Stark 2011). This age-related decline in high-interference memory makes it more difficult for older adults to retrieve relevant information in similar situations; critically, this can compromise decision-making (e.g., recalling whether the last dose of medication was taken today or yesterday) and social interactions (e.g., recognizing what information has already been conveyed to a person).
Although memory naturally declines with age, exercise may have the potential to slow the rate of decline (Bherer et al. 2013). Specifically, exercise mitigates age-related volume loss in brain regions implicated in memory function (Erickson et al. 2011) and enhances the functional connectivity of the white matter tracts to improve signal transduction (Fjell et al. 2014). These structural fortifications from exercise translate into functional improvements; for example, greater hippocampal cerebral blood volume is associated with better spatial memory (Erickson et al. 2011; Hillman et al. 2008; Honea et al. 2009), greater white matter integrity is associated with faster speed of information processing (Papp et al. 2014; Voss et al. 2010), and greater prefrontal cortical volume is associated with better general cognitive abilities such as inhibitory control, processing speed, and visuospatial processing (Colcombe et al. 2006).

Exercise also increases the production of new neurons in the hippocampus in animal models to bolster cognitive functions governed by the hippocampus, including learning and memory (Curlik and Shors 2013). One peripheral indicator of neurogenesis is brain derived neurotrophic factor (BDNF), which helps to support the growth and survival of neurons (Cotman and Berchtold 2002). Evidence from animal models suggests that BDNF is particularly important for high-interference memory, as it facilitates hippocampal neurogenesis (Bekinschtein et al. 2011). Aerobic exercise increases both BDNF protein and mRNA in the hippocampus of aged rats, and these increases are correlated with improved memory function (Fu et al. 2017). Similar findings are observed in younger human participants, with exercise increasing peripheral BDNF and high-interference memory (Déry et al. 2013). Likewise, in older humans participants, an acute bout of exercise can increase peripheral BDNF (Coelho et al. 2014); however, the impact of exercise and BDNF on high-interference memory for older adults has yet to be established.
The optimal intensity of aerobic exercise needed to improve memory and other cognitive functions is currently unknown. Low intensity walking has been shown to improve verbal memory, executive functions and processing speed (Papp et al. 2014; Scherder et al. 2014) as well as reduce dementia risk (Fenesi et al. 2016; Groot et al. 2016). Yet, evidence from younger adults suggests that higher intensity exercises, which are capable of inducing greater changes in cardiorespiratory fitness, may be needed to improve high-interference memory (Bherer et al. 2013; Déry et al. 2013; Heisz et al. 2017). This may be because high intensity exercise protocols induced greater increases in BDNF (Afzalpour et al. 2015; Marquez et al. 2015). Although cardiorespiratory fitness and cognitive performance are positively related in older adults as evidenced by observation studies (Bherer et al. 2013; Bullock et al. 2018), it is unclear whether higher intensity exercise causes greater improvements in high-interference memory and general cognitive functions (Sink et al., 2015; Young et al. 2015).

In addition to being a more potent physiological stimulus than low or moderate intensity exercise (Gibala and McGee 2008), high intensity exercise is also more time efficient. This has important implications for uptake by the older adult population. Regardless of one’s age, ethnicity, sex or health status, the most commonly cited reason for not exercising is a lack of time (Godin et al. 1994). Thus, an exercise prescription that requires minimal time commitment may be an effective approach to enhancing activity for this population (Gibala and McGee 2008). Similar to traditional moderate intensity endurance training (i.e., continuous brisk walking or jogging), high intensity exercise (i.e., at about 90% of maximum heart rate capacity) induces numerous metabolic adaptations in older adults including increased skeletal muscle oxidative capacity and endurance performance (Wyckelsma et al. 2017); the added benefit is that
high intensity exercise sessions are shorter in duration and require fewer sessions to yield positive results (Gibala and McGee 2008), and thus may be more feasible in the long term.

This community-based study investigated the effect of aerobic exercise intensity on cognition and BDNF in sedentary but otherwise healthy older adults. Participants were assigned to one of three intervention groups: a high intensity interval-training group (HIIT), a moderate intensity continuous training group (MCT), or a stretching control group (CON). High-interference memory was tested using an adapted mnemonic similarity task (Groot et al. 2016; Stark et al. 2015; Stark et al. 2013). Executive functions were examined using the Go-Nogo and Flanker tasks. Peripheral BDNF concentrations were quantified using enzyme-linked immunosorbent assays (ELISAs). We hypothesized that high intensity exercise training would lead to the greatest increases in BDNF and improvements in high-interference memory.

Materials and Methods

Participants

This community-based study took place over a period of approximately 2.5 years from August 2014 to March 2017. The methodology was originally reported in a master’s thesis (Kovacevic 2017) and is described in full below. A large effect size ($r^2 > 0.5$) was expected for the primary outcome based on a previous study using a high-interference memory task (Déry et al. 2013). The software G*Power was used to determine an adequate sample size of 64 participants needed to detect a significant difference between groups with $\beta = .8$ and $\alpha = .05$. Due to the rolling nature of the protocol, participants were over-recruited (n = 83) to account for dropouts.

Participants were recruited through local news outlets and postings. Participants consisted of sedentary, but otherwise healthy community-dwelling adults over the age of 60
years. Exclusion criteria included engaging in more than one hour of vigorous physical activity per week, or a diagnosis of cognitive impairment. The Montreal Cognitive Assessment (MoCA) (Nasreddine et al. 2005) was also used to assess baseline cognitive abilities; however, no one was excluded based on their score due difficulty in assigning a reliable and uniform cut-off across advancing age (Oren et al., 2015). Eligibility was assessed through verbal or written confirmation via phone or email. Potentially eligible participants completed a stress test with their physician prior to enrolment to screen for any abnormal response to physical exercise. Participants with abnormal responses were deemed ineligible. This study received ethics clearance from the Hamilton Integrated Research Ethics Board. All participants provided written informed consent prior to experimental procedures and were compensated $40 upon study completion.

Figure 1 depicts the overall design of the study. It is described in detail in the following sections.

[Insert Figure 1 here]

**Procedure**

The experimental procedure consisted of a pre and post intervention assessment that each took approximately two hours and included one hour of cognitive assessments, a half hour of physical and fitness assessments, and a half hour of questionnaire-based assessments. Post-testing was completed within 48 hours of the final intervention exposure.

Participants trained in one of three groups for the duration of the intervention: 1) High intensity interval training group (HIIT n=21), 2) Moderate-intensity continuous training group (MCT; n=20), or 3) Stretching exercise control group (CON; n=23). Participants were assigned to groups by a researcher. Group assignment was done according to blocks stratified by sex to
ensure equal distribution amongst groups. Due to equipment availability, group sizes were limited and therefore participants were assigned to the next available group if applicable. Group assignment took place prior to pre-intervention assessment, but participants did not learn their placement until assessments were completed, and all cognitive measures were objective to minimize bias of unblinding (Kahan et al. 2014). The training protocols and the measures used in the pre and post intervention assessments are described in the subsequent sections.

**Intervention Training**

The program was designed such that participants in all groups meet three times per week for 12 weeks for intervention training supervised by a trained research assistant. Participants were instructed not to engage in additional physical activity for the duration of the study. The 18th session was replaced with a midpoint exercise test resulting in a total target of 35 training sessions. To maximize retention, participants were accommodated for absences by continuing to meet with their respective intervention groups to make up missed sessions until they achieved as close to the target of 35 training sessions as possible (total weeks trained M=13, SD=3; total sessions completed M=34, SD=4). All participants completed at least half of the training protocol.

The HIIT and MCT training protocols were adapted from those described in Wisløff et al. (2007). To isolate the effect of intensity, the protocols were designed to be isocaloric and consequently their durations differed to match the total training load (Rognmo et al. 2004; Wisløff et al. 2007). Exercise training was completed on a motor-driven treadmill (Life Fitness 95Ti). The speed and incline of the treadmill were continually adjusted to ensure participants were training at their target heart rate, determined from the peak heart rate achieved in the fitness assessment, and target rating of perceived exertion (RPE) according to the Borg 6-to-20 scale.
(Borg 1982). If both target heart rate and target RPE were not achieved simultaneously, heart rate was the preferred indicator of intensity achieved.

**HIIT.** Participants warmed up for three minutes at 0% grade and 50-70% of peak heart rate, then 10 minutes at 5% grade and 60-70% of peak heart rate. Participants then walked four four-minute intervals at 5% grade and 90-95% of peak heart rate (target RPE=16-18+). These intervals were separated by three-minute active recovery periods where participants walked at 50-70% of peak heart rate (target RPE=9-11). After the final high-intensity interval, participants walked a three-minute cool-down at 50-70% of peak heart rate. A final two-minute cool-down was completed following the pre-programmed protocol on the treadmill. Total exercise time was 43 minutes. Heart rate and RPE were recorded at the end of each interval.

**MCT.** Participants warmed up for three minutes at 0% grade and 50-70% of peak heart rate before walking continuously at 70-75% of peak heart rate for 47 minutes (target RPE=12-14). A final two-minute cool-down was completed following the pre-programmed protocol on the treadmill, as above. Total exercise time was 52 minutes. Heart rate and RPE were recorded after the warm-up and every seven minutes for the remainder of the session.

**CON.** Participants engaged in a series of non-aerobic seated and standing stretches. The program was specifically designed for older adults and aimed at whole-body stretching. Each session was 30 minutes long. RPE was recorded after each 30-minute session. These sessions took place in a large classroom.

**Pre and Post Intervention Assessment**

**Memory.** High-interference memory was tested using an adapted *Mnemonic Similarity Task* (Groot et al. 2016; Stark et al. 2015; Stark et al. 2013). Participants began with an encoding phase in which 60 full color images of everyday objects on a white background were presented.
in random order on a computer screen for 2 seconds each. A blank screen preceded each trial for 500 milliseconds. Participants were instructed to classify each item as indoor or outdoor using the “1” and “2” keys, respectively, on the number pad. Immediately following the encoding phase, participants engaged in a forced-choice visual recognition phase, in which they classified items as “Old” (repetitions), “Similar” (lures), or “New” (foils) using the “1”, “2”, or “3” key, respectively, on the number pad. The recognition phase consisted of 90 trials presented in random order for an unlimited time until the participant responded: 30 stimuli were repeated from the encoding phase (repetitions), 30 were similar, but not identical (lures), and 30 were not previously viewed (foils). Performance on the task, corrected for response bias, was assessed using the lure discrimination index: the difference between the proportion of correctly identified lures as “Similar” minus the proportion of incorrectly classified foils as “Similar” \[ p(“Similar”|Lure) - p(“Similar”|Foil) \] (Stark et al. 2015; Stark et al. 2013).

The data were checked to ensure that participants performed the task correctly. Classifying foils as “New” is relatively simple, therefore participants who did not classify any foils as “New” were thought to not have understood the task instructions. One participant’s data for the MST were discarded for this reason.

**Executive functions.** Executive functions were tested using two computer tasks: the *Go-Nogo* task (Clark et al. 2015), and the *Flanker* task. In this task, participants were presented with 120 letters in white font on a black background in random order on a computer screen for 500 milliseconds each. They were instructed to respond as quickly as possible by pressing the space bar when they saw any letter (go trials) except for “A”, “S”, or “F” (nogo trials). The nogo trials comprised one third of the total number of trials. A blank screen preceded the presentation of a stimulus for a jittered duration between 500-1000 milliseconds.
For the Flanker task, a fixation cross was centered on the computer screen for one second, after which a single set of five arrows appeared for 50 milliseconds. The set was either congruent (i.e., “<<<<” or “>>>>”) or incongruent (i.e., “<><<” or “>>>>”). There were 90 trials in total and one third were incongruent. Participants were instructed to indicate whether the central arrow in the set pointed left or right by pressing the “z” or “/” key, respectively. There were an equal number of left and right target responses.

Performance on both executive functions tasks was assessed using an inverse efficiency score (IES) (Bruyer and Brysbaert 2011). The IES is calculated as the mean response time of the correct responses on go trials for the Go-Nogo and on incongruent trials for Flanker divided by the proportion of trials that were responded to correctly. By including accuracy, this calculation accounts for the controlled processing required to complete the task in addition to the speed of response.

Cardiorespiratory fitness. Fitness assessment to predict peak oxygen uptake (VO$_2$ peak) was performed at pre, mid, and post testing using a modified Bruce protocol on a motor-driven treadmill (Life Fitness 95Ti). Each stage of the protocol was three minutes long. Participants walked at a speed of 1.7 mph and 0% grade in the first stage, and 1.7 mph and 5% grade in the second stage, in accordance with the Bruce protocol modifications made by Willemsen et al. (2010). The remainder of the test followed the standardized Bruce protocol (Sheffield and Roitman 1976). A trained research assistant supervised the test and recorded time at exhaustion, heart rate at each interval and at exhaustion (measured using Polar FT1 heart rate monitors), and RPE at each interval according to the Borg 6-to-20 scale (Borg 1982). The test was terminated upon volitional exhaustion or presentation of abnormal symptoms. Predicted VO$_2$ peak was calculated using Equation 1 below, where the weighting factor was 1 for men and 2 for women.
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(Bruce et al. 1973). The duration used in the equation was that achieved on the standardized Bruce protocol, excluding the six minutes added as a result of the modification (Willemsen et al. 2010). Participants who did not complete protocol beyond the modification were excluded from fitness analyses (N=3). Since this protocol was a measure of predicted cardiorespiratory fitness, participants’ results (VO₂ peak and peak heart rate) on the modified Bruce protocol were correlated with performance on the exercise stress test, completed prior to study enrolment, to ensure that the predicted measures were valid.

\[
\text{Predicted VO}_2\text{peak} = 6.70 - 2.82 (\text{weighting factor for sex}) + 0.056 (\text{duration in seconds})
\]

Participants completed a familiarization at pre-test to get accustomed to walking on the treadmill and the full modified Bruce protocol was completed at a subsequent visit. During the familiarization, participants completed 9.5 minutes (the first 3 stages) of the modified Bruce protocol, unless volitional exhaustion was reached earlier. An additional fitness assessment was completed at midpoint to reassess peak heart rate and increase the difficulty of exercise training if a greater peak heart rate was achieved. The first 11 participants in the study completed the Single Stage Treadmill Walking Test, a submaximal cardiorespiratory fitness test (Ebbeling et al. 1991) instead of the maximal modified Bruce protocol, which was subsequently used for all participants upon additional ethics clearance for this specific protocol. Participants who completed the submaximal cardiorespiratory fitness test were excluded from analysis of cardiorespiratory fitness because cardiorespiratory fitness values obtained from the submaximal test did not correlate with those obtained from their physician’s stress test (\(p = .53\)) and therefore the values of the submaximal test were considered unreliable.

BDNF. Peripheral blood samples were collected from participants in the morning following 12 hours of fasting and prior to the cardiorespiratory fitness test described above.
Serum samples were obtained from whole blood collected in BD Vacutainer SST tubes (BD, Franklin Lanes, NJ, USA). Upon collection, the tubes were kept at room temperature for 30 minutes to clot and then were centrifuged at 4000 rpm for 10 minutes at 4°C. The supernatant was then aliquoted into Eppendorf tubes and stored at -80°C until analysis.

Serum BDNF concentrations were quantified using an enzyme-linked immunosorbent assay (ELISA) according to kit specifications using the human free BDNF Quantikine ELISA kit (R&D Systems; Minneapolis, MN, USA; cat#SBD00). All samples and standards were run in duplicate and the optical density of samples was determined after ten minutes of adding Stop Solution at 450 nm with wavelength correction set to 540 nm. Samples were measured using BioTek’s Synergy Mx Microplate Reader and Gen5 1.11 Microplate Reader and Imager Software (BioTek).

Statistical Analyses

Data were checked for outliers and normality, and to ensure appropriate assumptions were met for each analysis. Outliers were defined as values beyond quartiles 1 (Q1) and 3 (Q3) with a step of 1.5 times the interquartile range (IQR; i.e., values <Q1–1.5IQR or >Q3+1.5IQR). Overall, there were very few outliers, which were removed pairwise (cardiorespiratory fitness: HIIT=1; memory: MCT=2, CON = 1; Flanker: HIIT=3; BDNF: HIIT=1). Change scores collapsed across group were also independently evaluated for outliers, with few outliers removed pairwise (memory: CON=1; GoNogo: CON=1; Flanker: HIIT=1, CON=2; BDNF: MCT=3, CON=4). Normality was assessed by histograms and significance on the Kolmogorov-Smirnov test. Only the Flanker results were non-normal and reciprocally transformed prior to analysis. Homogeneity of variance was assessed using Levene’s test for ANCOVAs.
As a manipulation check, the mean number of sessions attended, and heart rate and RPE during exercise were calculated to ensure that the intended prescription was achieved.

To confirm that the interventions induced the expected fitness adaptations from pre- to post-test, a univariate ANCOVA was conducted on post-test predicted VO$_2$ peak values with a between-subjects factor of group, and with age and pre-test predicted VO$_2$ peak values entered as covariates. To verify that the modified Bruce protocol used in this study was a valid measure of both cardiorespiratory fitness and peak heart rate, two two-tailed partial correlations, controlling for age, were conducted: one between predicted VO$_2$ peak achieved on the modified Bruce protocol and VO$_2$ peak achieved on the stress test, and one between peak heart rate achieved on the modified Bruce protocol and peak heart rate achieved on the stress test.

To evaluate how exercise intensity affected cognitive performance, univariate ANCOVAs were conducted on the post-test scores of each measure using a between-subjects factor of group. Age and pre-test scores were used as covariates. Post hoc pairwise comparisons were performed to examine group effects.

Based on prior research, we hypothesized that increases in fitness would lead to monotonic improvements cognition (Bullock et al. 2018). To examine this, we conducted one-tailed Spearman’s correlations between VO$_2$ peak change scores and change scores for each cognitive outcome collapsed across all groups. All change scores were determined by subtracting pre-test values from post-test values.

**Results**

Participant flow through the study is presented in Figure 2. A total of 83 interested and eligible participants attended the pre-testing session. Five participants withdrew before training and thus 78 were enrolled in the study. Thirteen participants (17%) withdrew during training
(HIIT=3, MCT=5, CON=5). One participant was excluded from analysis upon becoming ineligible near study completion because their physician diagnosed them with mild cognitive impairment. This resulted in 64 participants (61% females; mean age=72 years; age range=60-88 years) who completed the study and were included in the analysis.

Baseline demographic data are represented in Table 1. Predicted VO$_2$ peak on the modified Bruce protocol was significantly correlated with VO$_2$ peak from the stress test ($p < .001$). Peak heart rate achieved on the modified Bruce protocol was significantly correlated with peak heart rate from the stress test ($p < .001$).

**Manipulation check**

All analyzed data met the outlined assumptions including normality and homogeneity of variance. Data from the Flanker task were positively skewed and were reciprocally transformed to a normal distribution.

Exercise training characteristics are presented in Table 2. Although RPE was lower than expected for the desired intensity, target heart rate was used as the primary indicator of intensity.

**Cardiorespiratory fitness.** The interventions induced cardiorespiratory fitness adaptations from pre- to post-test, such that exercise training led to the greatest increases in predicted VO$_2$ peak [$F(2, 43) = 26.45, p < .001, \eta_p^2 = .55$]. Pairwise comparisons revealed that both HIIT (29.8 ± 4.9) and MCT (30.3 ± 3.8) had greater predicted VO$_2$ peak at post-test than CON (18.7 ± 6.8; HIIT vs. CON: $p < .001$; Cohen’s $d = 1.9$; MCT vs. CON: $p < .001$, Cohen’s $d = 2.1$). There were no differences between HIIT and MCT ($p = .83$).
Group-based analyses

**Memory.** Figure 3 depicts high-interference memory performance across groups. There was a significant main effect of group on high-interference memory \( F(2, 55) = 6.04, p = .004, \eta^2_p = .18 \). Pairwise comparisons revealed that HIIT induced better memory performance than MCT (Cohen’s \( d = 1.2, p = .003 \)) and CON (Cohen’s \( d = 1.1, p = .004 \)) but MCT and CON were not significantly different from each other (\( p = .85 \)).

As depicted in Figure 4, increases in predicted VO\(_2\) peak was positively correlated with improvements in high-interference memory performance with a medium effect size \( r_s(46) = .27, p = .03 \).

[Insert Figure 3 and 4 here]

**Executive functions.** For the Go-Nogo task, there was a trend towards a main effect of group \( F(2, 59) = 2.54, p = .088, \eta^2_p = .08 \). Both HIIT and MCT had a trend toward inducing better performance than CON with moderate effect sizes (HIIT vs. CON: Cohen’s \( d = .7, p = .056 \); MCT vs. CON: Cohen’s \( d = .7, p = .057 \)). There were no differences between HIIT and MCT (\( p = .99 \)).

For the Flanker task, there was also trend towards a main effect of group \( F(2, 56) = 2.41, p = .099, \eta^2_p = .08 \). HIIT had a trend toward inducing better performance than both MCT (Cohen’s \( d = .7, p = .072 \)) and CON (Cohen’s \( d = .7, p = .049 \)) with moderate effect sizes. There was no significant difference between MCT and CON (\( p = .91 \)).

Increases in predicted VO\(_2\) peak tended to correlate with improvements in performance efficiency on the Go-Nogo task with a medium effect size but not significant \( r_s(46) = -.23, p = .06 \), but there was no correlation with the Flanker task \( r_s(47) = -.02, p = .44 \).
**BDNF.** Table 3 presents BDNF values across groups. There was no main effect of group on BDNF \[ F(2, 54) = .21, p = .81 \]. Change in BDNF did not correlate with change in predicted VO2 peak \[ r_s(38) = -.16, p = .32 \] or change in memory \[ r_s(50) = .04, p = .79 \]. Likewise, baseline BDNF did not correlate with change in predicted VO2 peak \[ r_s(45) = .14, p = .34 \] or change in memory \[ r_s(57) = -.01, p = .93 \].

**Discussion**

Higher intensity exercise improved memory in sedentary older adults over a relatively short 12-week intervention. This is in contrast to more traditional forms of moderate continuous exercise that had no effect on memory at the group level. Furthermore, improvements in cardiorespiratory fitness correlated with improvements in memory, suggesting that adaptations in the utilization of oxygen during exercise may influence brain function in aging.

High-interference memory significantly improved following HIIT but not MCT (Figure 3). This is an important finding because it helps to clarify inconsistencies in the literature with respect to exercise and memory (Asl et al. 2008; Clark et al. 2015; Creer et al. 2010; Erickson et al. 2011; Heisz et al. 2015). Specifically, the present study suggests that exercise intensity may be a critical factor. Previous interventions of similar duration (~12 weeks) but using low-to-moderate intensity exercise have failed to demonstrate memory improvements in older adults (Iuliano et al. 2017; Perri and Templer 1985). Although these studies would suggest that memory improvements may not be possible following such short interventions, we recently demonstrated that only six weeks of high-intensity exercise training improved memory in young adults (Heisz et al. 2017). Therefore, the present study provides novel data demonstrating that exercise can improve memory in older adults over a short intervention, but that the exercise may need to be of higher intensity.
At the individual level, we observed a significant correlation between increases in cardiorespiratory fitness and improvements in memory (Figure 4). Data points for MCT overlapped with HIIT and so despite robust group level differences favoring HIIT over MCT, MCT may be of sufficient intensity to enhance memory for some. Interestingly, many individuals in the CON group had declines in both fitness and memory. This observation suggests that some exercise, even if not enough to enhance memory, may help mitigate age-related decline in fitness to prevent memory loss.

In contrast, exercising at either moderate or high intensity had a moderate-sized but nonsignificant effect on executive functions. Prior interventions of longer duration (i.e., lasting at least 6 months) that have used moderate intensity exercise and found similar but significant improvements in executive functions in older adults (Colcombe et al. 2004; Kramer et al. 2001). Critically, the moderate effect of HIIT and MCT on executive functions was different from the robust benefit effect of HIIT on high-interference memory and suggests that exercise intensity may differentially impact these cognitive functions. Indeed, brain processes that subserve executive functions and memory seem to respond differently to increasing exercise intensity and this may be related to their sensitivity to physiological stress. For example, the prefrontal cortex (PFC) is recruited for executive functions. Moderate intensity exercise—a moderate physiological stressor—evokes a more positive effect on executive functions than more vigorous exercise (Chang et al. 2012; Labelle et al. 2013). Likewise, activation of the PFC also follows an inverted-U shaped curve such that a moderate stressor increases glutamatergic transmission to enhance executive functions (Yuen et al. 2009) whereas a severe stressor impedes this process (Hains and Arnsten 2008). Although we observed similar effects of both moderate and high intensity exercise on executive functions, the interval structure of our high intensity exercise
protocol (i.e., including rest breaks between intense bouts) may have made it overall less severe, and thus still within the positive range.

BDNF has been identified as a potential mechanism for the effects of exercise on memory. Unlike the inverted U activation pattern of the PFC, the relationship between exercise intensity and BDNF seems to be more linear, such that higher intensity exercises elicit greater BDNF (Ferris et al. 2007; Gold et al. 2003; Saucedo Marquez et al. 2015; Schmidt-Kassow et al. 2012; Vega et al. 2006). Prior work in older adults has demonstrated that high intensity exercise can increase BDNF to improve memory (De Assis and Almondes 2017); however, that was not the case here such that we observed significantly group differences in memory but no group differences in BDNF. Although the results suggest that BDNF may not be mediating these cognitive improvements, this is opposite to many reports in the literature (De Assis and Almondes 2017; Szuhany et al. 2015). Alternatively, it is also possible that the null findings may be due to the timing of blood sample collection. In previous studies showing exercise-induced increases in BDNF (Ferris et al. 2007; Schmidt-Kassow et al. 2012), blood samples were collected within one hour following an exercise bout. Indeed, exercise-induced increases in BDNF tend to return to baseline within minutes to a few hours following an acute exercise bout (Vega et al. 2006). Our blood samples were collected 24 to 48 hours after the final exercise exposure, therefore, any transient changes in BDNF from an acute bout of exercise would have returned to baseline by the time the samples were collected. Although we were hoping to capture adaptations in the resting state levels of BDNF from the chronic training program, the results suggest that the neurotrophic effects of exercise may be closely tied to the acute stimulation from the exercise bout itself rather than adaptations in the baseline state. Future research is needed to contrast the impact of exercise training on BDNF levels during the acute phase following a bout.
of exercise as well as at rest. In addition, there may be other biochemical factors, besides BDNF, that underlie the effect of exercise on memory. One theory based on recent evidence is that HIIT, being a more intense stimulus than MCT, increases lactate levels to a greater extent. Lactate is an important factor for promoting neuroplasticity (El Hayek et al. 2019) and may support our finding of memory improvement following HIIT. Future studies should also include a measure of lactate to further investigate this potential mechanism.

Overall, this community study provides critical information about the implementation of exercise programs for memory, but it is not without limitations. The first wave of participants (n=11) was not included in our assessment of cardiorespiratory fitness because they did not complete the maximal aerobic fitness test, and thus were treated as missing data. However, the missing data were distributed across all three groups and so was unlikely to impact the results. Additionally, participants were classed as sedentary if they reported engaging in less than one hour of vigorous physical activity per week. While this cut-off is below the 150 minutes of moderate-to-vigorous aerobic exercise weekly recommended for adults 65 years and older by the Canadian Society for Exercise Physiology (CSEP 2011), self-reports by participants may not have most accurately captured true baseline activity levels. We also had broad inclusion criteria to be more realistic of a community-based program, including people on beta-blockers, which can interfere with accurate heart rate reading. Although we used both heart rate and RPE as indicators of intensity, it should be noted that the HIIT group had no participants known to be on beta-blockers and this may have resulted in a more accurate estimate of heart rate for that group.

With the rapidly growing population of older adults and increasing prevalence of neurodegenerative disease, it is essential to identify effective interventions for promoting cognitive function. This community-based study provides much needed evidence regarding the
effect of exercise intensity on cognitive functions among older adults and helps inform possible mechanisms for mitigating cognitive decline and potentially dementia risk. Overall the findings suggest that a relatively short-term program of high-intensity interval exercises may help older adults improve memory, and thus may represent as an effective strategy for promoting physical fitness and brain health in aging. Future directions include investigating more direct measures of memory, such as anterior and posterior hippocampal volume following HIIT versus MCT to confirm exercise-induced changes in brain physiology. Additionally, it would be important to investigate the acute time course of BDNF following HIIT versus MCT, as well as other potential molecular regulators such as lactate.

Acknowledgements

We would like to thank the NeuroFitLab members and the McMaster Physical Activity Centre of Excellence (PACE) faculty and staff who helped facilitate the project. Most of all, we are grateful to the participants who dedicated their time to take part in this study.

Funding

This research was supported by the Alzheimer Society of Brant, Haldimand, Norfolk, Hamilton and Halton, Banting Foundation Discovery Award, and Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant 296518 to Jennifer J. Heisz. Ana Kovacevic was supported by a Canada Graduate Scholarship-Master’s from NSERC.

Conflicts of Interest

The authors have no conflicts of interest to report.
References


Bruyer, R., and Brysbaert, M. 2011. Combining speed and accuracy in cognitive psychology: is the inverse efficiency score (IES) a better dependent variable than the mean reaction time (RT) and the percentage of errors (PE)? Psychol. Belg. 51(1): 5-13. doi: 10.5334/pb-51-1-5.


Tables

Table 1. Demographic characteristics at baseline across groups

<table>
<thead>
<tr>
<th></th>
<th>HIIT (N=21)</th>
<th>MCT (N=20)</th>
<th>CON (N=23)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72.4 (4.4)</td>
<td>72.0 (6.2)</td>
<td>71.5 (6.6)</td>
<td>.87†</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>14</td>
<td>10</td>
<td>15</td>
<td>.48‡</td>
</tr>
<tr>
<td>MoCA (max score = 30)</td>
<td>25 (3)</td>
<td>26 (3)</td>
<td>26 (2)</td>
<td>.53†</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>27 (4)</td>
<td>28 (4)</td>
<td>30 (6)</td>
<td>.18†</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>138.7 (17.8)</td>
<td>139.7 (23.8)</td>
<td>140.2 (19.4)</td>
<td>.97†</td>
</tr>
<tr>
<td>Diastolic</td>
<td>73.1 (9.3)</td>
<td>71.3 (11.1)</td>
<td>69.0 (8.6)</td>
<td>.37†</td>
</tr>
<tr>
<td>β-blockers</td>
<td></td>
<td></td>
<td></td>
<td>.35‡</td>
</tr>
<tr>
<td>No</td>
<td>16</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Predicted VO₂ peak (ml/(kg•min))*</td>
<td>25.0 (6.2)</td>
<td>24.9 (5.5)</td>
<td>19.2 (6.7)</td>
<td>.009†</td>
</tr>
<tr>
<td>Stress test VO₂ peak (ml/(kg•min))*</td>
<td>21.1 (3.0)</td>
<td>20.4 (4.1)</td>
<td>18.1 (3.7)</td>
<td>.07†</td>
</tr>
<tr>
<td>Peak heart rate (bpm)*</td>
<td>142.7 (12.9)</td>
<td>138.5 (14.5)</td>
<td>134.0 (24.2)</td>
<td>.37†</td>
</tr>
<tr>
<td>Stress test peak heart rate (bpm)*</td>
<td>142.9 (17.0)</td>
<td>137.7 (19.2)</td>
<td>129.7 (23.7)</td>
<td>.11†</td>
</tr>
</tbody>
</table>

Note. Data represented are mean and standard deviation (SD) or number of participants. MoCA: Montreal Cognitive Assessment (Nasreddine et al. 2005); bpm: beats per minute. *means and SD based on fewer number of participants with available data (Predicted VO₂ peak, HIIT=17, MCT=17, Control=18; Stress test VO₂ peak, HIIT=15, MCT=12, CON=15; Peak heart rate, HIIT=17, MCT=17, CON=18; Stress test peak heart rate, HIIT=20, MCT=20, CON=22).
† One-way ANOVA
‡ Pearson Chi-Square
Table 2. Intervention training characteristics across groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HIIT (N=21)</th>
<th>MCT (N=20)</th>
<th>CON (N=23)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training sessions attended</td>
<td>33.8 (3.6)</td>
<td>32.5 (5.1)</td>
<td>34.9 (1.7)</td>
<td>.11†</td>
</tr>
<tr>
<td>Number of weeks attended</td>
<td>12.9 (2.6)</td>
<td>12.5 (3.2)</td>
<td>13.9 (2.0)</td>
<td>.21†</td>
</tr>
</tbody>
</table>

Session heart rate

<table>
<thead>
<tr>
<th></th>
<th>HIIT (N=21)</th>
<th>MCT (N=20)</th>
<th>CON (N=23)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean heart rate</td>
<td>125.1 (9.2)</td>
<td>104.8 (11.9)</td>
<td>N/A</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Mean percentage of peak</td>
<td>87.4 (3.6)</td>
<td>74.6 (5.2)</td>
<td>N/A</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Mean session RPE (6-20)</td>
<td>12.9 (1.9)</td>
<td>9.3 (1.6)</td>
<td>8.3 (1.7)</td>
<td>&lt;.001†a</td>
</tr>
</tbody>
</table>

Note. Data represented are mean and standard deviation (SD). N/A: not applicable; RPE: Rated perceived exertion.

† One-way ANOVA

*Independent samples T Test

a HIIT>MCT (\( p<0.001 \)), HIIT>CON (\( p<0.001 \)), MCT>CON (\( p=0.075 \))
Table 3. Mean (SD) for cardiorespiratory fitness, cognition and BDNF at pre- and post-test across groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HIIT</th>
<th>MCT</th>
<th>CON</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
</tr>
<tr>
<td><strong>Cardiorespiratory Fitness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted VO&lt;sub&gt;2&lt;/sub&gt; peak (ml/(kg•min))</td>
<td>17</td>
<td>25.0 (6.2)</td>
<td>15</td>
<td>29.8 (4.9)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>17</td>
<td>24.9 (5.5)</td>
<td>17</td>
<td>30.3 (3.8)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18</td>
<td>19.2 (6.7)</td>
<td>16</td>
</tr>
<tr>
<td><strong>Cognition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-interference memory</td>
<td>21</td>
<td>0.26</td>
<td>21</td>
<td>0.34 (0.14)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>19</td>
<td>0.24</td>
<td>17</td>
<td>0.17 (0.14)</td>
<td>22</td>
<td>0.12</td>
<td>22</td>
</tr>
<tr>
<td>Go IES (ms)</td>
<td>21</td>
<td>494 (66)</td>
<td>21</td>
<td>488 (51)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>19</td>
<td>(0.24)</td>
<td>20</td>
<td>485 (64)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>23</td>
<td>(0.12)</td>
<td>23</td>
</tr>
<tr>
<td>Go reaction time (ms)</td>
<td>21</td>
<td>479 (56)</td>
<td>21</td>
<td>484 (51)</td>
<td>19</td>
<td>482 (57)</td>
<td>20</td>
<td>462 (51)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>23</td>
<td>507 (63)</td>
<td>23</td>
</tr>
<tr>
<td>Go accuracy (%)</td>
<td>21</td>
<td>97 (3)</td>
<td>21</td>
<td>99 (1)</td>
<td>19</td>
<td>96 (5)</td>
<td>20</td>
<td>96 (5)</td>
<td>23</td>
<td>97 (3)</td>
<td>23</td>
</tr>
<tr>
<td>Flanker IES (ms)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>21</td>
<td>1863 (2140)</td>
<td>18</td>
<td>818 (174)&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>20</td>
<td>1505 (1431)</td>
<td>20</td>
<td>1274 (920)</td>
<td>23</td>
<td>1368 (1064)</td>
<td>23</td>
</tr>
<tr>
<td>Flanker reaction time (ms)</td>
<td>21</td>
<td>905 (526)</td>
<td>18</td>
<td>686 (133)</td>
<td>20</td>
<td>954 (510)</td>
<td>20</td>
<td>865 (315)</td>
<td>23</td>
<td>887 (429)</td>
<td>23</td>
</tr>
<tr>
<td>Flanker accuracy (%)</td>
<td>21</td>
<td>71 (24)</td>
<td>18</td>
<td>85 (8)</td>
<td>20</td>
<td>77 (19)</td>
<td>20</td>
<td>78 (17)</td>
<td>23</td>
<td>78 (23)</td>
<td>23</td>
</tr>
<tr>
<td>BDNF (ng/mL)</td>
<td>19</td>
<td>29.5 (6.8)</td>
<td>19</td>
<td>27.6 (6.7)</td>
<td>19</td>
<td>29.1 (7.9)</td>
<td>19</td>
<td>26.0 (7.8)</td>
<td>22</td>
<td>24.6 (10.4)</td>
<td>21</td>
</tr>
</tbody>
</table>

Note. Data are represented with mean and standard deviation (SD); RT = reaction time; IES = inverse efficiency score

<sup>a</sup> significantly different from MCT (p<0.05)
<sup>b</sup> significantly different from CON (p<0.05)
<sup>c</sup> trending difference from MCT (p<0.1)
<sup>d</sup> trending difference from CON (p<0.1)
<sup>e</sup> analysis conducted on reciprocally transformed data, means reflect raw values with outliers from analysis removed
Figure Captions

Figure 1. Schematic of study design.

Figure 2. Flow of participants through study protocol.

Figure 3. Mean high-interference memory performance for high-intensity interval training (HIIT), moderate continuous training (MCT) and control (CON) at post-test. Covariates appearing in the model were evaluated at the following values: Age = 72, pre-test = 19. **p < .01. Bars represent standard error.

Figure 4. Association between change in cardiorespiratory fitness and memory performance across high-intensity interval training (HIIT), moderate continuous training (MCT) and control (CON): r(46) = .27, p = .03.
Pre-Intervention Assessment

Intervention training (12 weeks)

<table>
<thead>
<tr>
<th>HIIT (43min)</th>
<th>MCT (52min)</th>
<th>CON (30min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warm-up</strong></td>
<td><strong>Warm-up</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Interval (4min) x4</strong></td>
<td><strong>Continuous walking (47min)</strong></td>
<td><strong>Whole-body stretching (30min)</strong></td>
</tr>
<tr>
<td>Target HR: 90-95% peak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target RPE: 16-18+</td>
<td>Target HR: 70-75% peak</td>
<td></td>
</tr>
<tr>
<td>Target RPE: 9-11</td>
<td>Target RPE: 12-14</td>
<td></td>
</tr>
<tr>
<td><strong>Recovery (3min) x4</strong></td>
<td><strong>Cool-down</strong></td>
<td></td>
</tr>
<tr>
<td>Target HR: 50-70% peak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPE: 9-11</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cool-down</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Post-Intervention Assessment

Figure 1. Schematic of study design.
Figure 2. Flow of participants through study protocol.
Figure 3. Mean high-interference memory performance for high-intensity interval training (HIIT), moderate continuous training (MCT) and control (CON) at post-test. Covariates appearing in the model were evaluated at the following values: Age = 72, pre-test = 19. **p < .01. Bars represent standard error.
Figure 4. Association between change in cardiorespiratory fitness and memory performance across high-intensity interval training (HIIT), moderate continuous training (MCT) and control (CON): rs(46) = .27, p = .03.