Performance on an associative memory test decreases 8 hours after cardiovascular exercise

Date of Submission: Aug 27th, 2019

Abstract

The present study was designed to assess the effects of acute exercise on performance of a paired associate learning [PAL] test, an operationalization of hippocampal-dependent associative memory. Participants performed a PAL test, then ran on a treadmill (exercise group, n=52) or solved Sudoku puzzles (control group, n=54). Participants returned 2, 5, or 8 hrs later to perform a second, different, PAL test. PAL scores for the control group did not change over time. Similarly, scores on tests taken 2 and 5 hrs after exercise were not different from baseline, or control data. Scores on tests taken 8 hrs after exercise, however, fell significantly below baseline (by 8.6%) and control (by 9.8%) scores. These data demonstrate that acute exercise can negatively impact the encoding and retrieval of new information even hours after the exercise bout, which should be a consideration when designing exercise programs to enhance, and not hinder, learning.

Introduction

While the physical benefits of cardiovascular exercise have long been known (Siscovick, Laporte, & Newman, 1985; Sothern, Loftin, Suskind, Udall, & Blecker, 1999; Warburton, Nicol, & Bredin, 2006), it is becoming increasingly clear that exercise can also have diverse cognitive benefits (see Roig, Nordbrandt, Geertsen, & Nielsen, 2013; Tomporowski & Ellis, 1986, for review). In fact, even a single bout of exercise ("acute" exercise) can improve performance on tests of long-term memory (Coles & Tomporowski, 2008; Labban & Etnier, 2011; McNerney & Radvansky, 2015; Segal, Cotman, & Cahill, 2012; Winter et al., 2007). The current thinking is that after exercise, transient changes in concentrations of neurochemicals such as lactate, noradrenaline, endocannabinoids, and brain derived neurotropic factor [BDNF] and glycogen (Bosch et al., 2017; Cotman & Berchtold, 2002; Knaepen, Goekint, Heyman, & Meeusen, 2010; Oz et al., 2009, Segal et al., 2012; Skriver et al., 2014) strengthen encoding and consolidation of long-term memory (Chang, Labban, Gapin, & Etnier, 2012; Labban & Etnier, 2011; Segal et al., 2012; Skriver et al., 2014; van Dongen, Kersten, Wagner, Morris, & Fernández, 2016). Ultimately, these exercise-induced increases in neurochemicals may help facilitate long-term potentiation [LTP], a cellular correlate for episodic memory (Poo et al., 2016). Although acute exercise has been demonstrated to reliably increase LTP in animal models, the data from human experiments is limited (see Loprinzi, 2019a for review). The relatively short time-course of increases in lactate, noradrenaline, and endocannabinoids, on the scale of ~10–60 mins (Ferris, Williams, & Shen, 2007; Knaepen et al., 2010; Skriver et al., 2014; Tang, Chu, Hui, Helmeste, & Law, 2008), and corresponding improvements in performance on tests of long term memory over this interval (Coles & Tomporowski, 2008; Labban & Etnier, 2011; Potter & Keeling, 2005; Winter et al., 2007; Segal et al., 2012; see

below), have led to the idea that the benefits of acute exercise on memory are limited to when the exercise is performed in close temporal proximity to the encoding of new memory (Crush & Loprinzi, 2017; Roig et al., 2013, 2016). However, the time scale of changes after exercise in other neurochemicals such as BDNF (Castellano & White, 2008; Yarrow et al., 2008) and glycogen (Matsui et al., 2012, Oz et al., 2009) is much longer. The extent of BDNF's effect on mediating the relationship between exercise and memory in human models is unclear (Loprinzi, 2019b), while the effect of longer lasting changes in glycogen remains unexplored.

Many of the demands on memory during everyday life are contextually specific, relational, and depend on generalization, all functions thought to involve the hippocampus (Eichenbaum, 2009). Several studies have shown that acute exercise improves performance on memory tasks that involve the hippocampus such as free recall (Coles & Tomporowski, 2008; Labban & Etnier, 2011; Potter & Keeling, 2005; Winter et al., 2007) and image recall (Segal et al., 2012), when the encoding of the new memory is performed one hour or less after exercise. Only one study has explored the effects of acute exercise on encoding and retrieval on a timescale longer than one hour in humans. Basso et al. (2015) found that 2 hrs after exercise, tests of hippocampal function such as long-term memory and pattern separation were not different from pre-exercise, control data. In that study, both the encoding and retrieval phases of the memory task were performed prior to and after the exercise. Thus, there is ample evidence indicating that encoding and retrieval of new hippocampal-dependent memories are enhanced within 1 hr after exercise and one study suggests that this ability is not enhanced 2 hrs after exercise (Basso et al., 2015). Two studies have shown improvements in memory 2 hrs (Bosch et al., 2017) or 4 hrs (van Dongen et al. 2016) after exercise. However, in both studies the exercise was performed in between

encoding and retrieval and thus the focus of those studies was on the consolidation and retention of already existing memories. No study has investigated the extent to which exercise influences the subsequent encoding and retrieval of new memories on a time scale longer than 2 hrs after acute exercise.

The present study was designed to explore the effects of acute exercise on the ability to encode and retrieve new information over a time scale longer than had been tested previously. Encoding and retrieval of associative memory was assessed from 2-8 hrs after exercise, as this is an interval over which there are changes known neurochemicals that are important for memory (Castellano & White, 2008; Matsui et al., 2012) and it allowed us to explore how exercise may influence memory over the course of a typical 8 hr workday. Participants completed the first paired associate learning (PAL) test before either running on a treadmill (exercise group) or playing Sudoku (control group). The PAL test is thought to be an operationalization of hippocampal-dependent associative memory (Caplan & Madan, 2016). For each test, participants were presented with 10 pairs of words, then, after a distractor task, they were given a list of 10 single words and were asked to recall the missing words. This was repeated 4 times (i.e., 4 groups of 10 word-pairs) and comprised the first PAL test. The second PAL test was completed either 2, 5, or 8 hrs after the exercise or control task. It was unique from the first, as different words were used. Using this study design, which is similar to Basso et al. (2015), enabled us to specifically assess the influence of acute exercise on the encoding and retrieval of new memories. Scores for participants in the exercise group were compared to their own scores at baseline and to the scores of the control group at the same delay. The results of these experiments contribute to our understanding of the time course over which acute exercise influences hippocampal-dependent associative memory.

Materials and Methods

Participants

Participants were recruited from the Department of Psychology research subject pool at the University of Alberta in exchange for course credit, or were volunteers recruited from the general university population. All procedures were approved by the University of Alberta Human Research Ethics panel. Participants were excluded if they had learned English after the age of 5, if they reported that they had a disorder or condition that impairs learning, if they reported exercising in the morning prior to the first session, or if responses to the Physical Activity Readiness Questionnaire identified any factor that would prevent them from exercising. Based on these criteria, 112 individuals were enrolled in the study and took part in two experimental sessions both on the same day, either 2, 5 or 8 hrs apart. When enrolling, participants selected to be in either the 2, 5, or 8-hr subgroup without knowing the study, and were then randomly assigned to the exercise or control group. Between sessions, they were free to carry on with their normal routine. When participants returned for the second session they were asked if they had exercised in the interval. The self-selection of delay group (i.e. 2, 5, or 8 hrs), and the lack of activity restriction in the interim between the first and second PAL test were conditions of research as per the University of Alberta Human Research Ethics Panel. After data were collected, 4 participants were removed from the analyses because they reported exercising between the morning and afternoon sessions and data from an additional 2 participants were removed because after completing the study, in the second session, those individuals reported previously undisclosed exclusion criteria. Thus, data from 52 participants in the exercise group and 54 participants in the control group were included in the final analyses (n=106; 20.3 ± 0.28 years; 48 men and 58 women). To assess baseline physical activity levels of all participants, the Godin-

Shephard Leisure-Time Physical Activity Questionnaire [GSLTPAQ] was administered

(Godin & Shephard, 2011). The relationship between GSLTPAQ score and physical

fitness indicators (VO_2 max, % of body fat, BMI) has been previously validated for the

use of ranking activity levels in healthy adults (Amireault & Godin, 2015; Godin &

Shephard, 1985; Jacobs, Ainsworth, Hartman, & Leon, 1993). The average ages, gender

distributions, and GSLTPAQ score for each subgroup are reported in Supplementary

Table 1A. Age did not vary by group [$F_{(1, 99)}$=0.182, p=0.670] or delay [$F_{(2, 99)}$=0.638,

p=0.538]. Gender did not vary by group [$F_{(1, 100)}$=1.321, p=.253] or delay [$F_{(2, 100)}$=0.137, p=0.872]. Scores on the GSLTPAQ score did not vary by group [$F_{(1, 100)}$=1.393, p=0.241] or delay [$F_{(2, 100)}$=1.133, p=0.710], and all participant groups were

considered "active" (score >24).

General Procedure

The first of the two sessions started for all participants between 8:30–9:30 am and lasted

approximately 50 mins. In this session participants first performed a baseline PAL test

(described below) and then, within approximately 1 minute, the exercise group ran on a

treadmill for 20 mins and the control group played Sudoku puzzles for 20 mins (from

www.websudoku.com; see below for details). Participants then returned for their second

session after a delay of 2 (exercise group n=17, control group n=18), 5 (exercise group

n=19, control group n=18) or 8 hrs (exercise group n=16, control group n=18) (see Fig

1). During the second session participants completed a second PAL test, using entirely

different words than the baseline test. Using this experimental design, encoding and

retrieval occurred in close proximity to each other (within approximately 2 mins), and

thus both were completed before the exercise or control task for the baseline PAL test,

and at variable delays after the exercise or control task for the second PAL test.

Exercise Task

Participants in the exercise group ran on a treadmill for 20 mins at an incline of 3

degrees and an initial speed of 3.0 mph. Treadmill speed was increased to 5.5 mph in

0.5 mph increments at one-minute intervals over the first 5 mins for warm up. During

the last minute of exercise, treadmill speed was lowered to 1.5 mph over ~5 seconds for

cool-down. This exercise task was adapted from the protocol used by Tomporowski et

al. (Tomporowski, Ellis, & Stephens, 1987). Heart rate was measured (Polar FT1 heart

rate monitor) while participants stood on the treadmill before exercising and once a

minute during the exercise task. The goal was to maintain a heart rate between 70–85%

of each participant's age-predicted maximum heart rate for a minimum of 10 mins. This

range of heart rates was chosen because it is considered to represent vigorous exercise

by the Centers for Disease Control and Prevention (Centers for Disease Control and

Prevention, 2015) and high-intensity exercise has been shown to be more beneficial

than moderate intensity exercise for hippocampal-dependent memory tasks (Loprinzi,

2018). Age-predicted maximum heart rate was calculated as 220 minus the age of the

participant (Centers for Disease Control and Prevention, 2015). If a participant's heart

rate increased to more than 90% of their age-predicted maximum, treadmill speed was

decreased by 1.0 mph to prevent their further increases in heart rate. After completion

of the task, participants completed the Borg Scale Rating of Perceived Exertion to

determine their subjective perception of level of exertion during the exercise bout. Borg

Scale scores range from 6-20, with 6 representing no exertion and 20 representing

maximal exertion (Centers for Disease Control and Prevention, 2015). Data from five

participants were excluded from the heart rate analyses due to difficulties obtaining the

heart rate measurements while participants ran on the treadmill.

Control Task

Participants in the control group played a medium-difficulty Sudoku puzzle from www.websudoku.com for 20 mins and heart rate was measured before starting the puzzle and once a minute during the task. This was chosen as an active control as in the study by McNerney and Radvansky (2015). In addition, solving Sudoku puzzles, reading neutral text, and video watching as controls in a similar acute exercise-memory protocol have all been shown to not influence memory performance (Blough & Loprinzi, 2019). A cognitively disengaging task, such as quiet rest, was not chosen as the length of our control task was 20 minutes. Similar to Loprinzi and Blough (2019), we thought this was likely to induce participant boredom and frustration that would have reduced overall compliance rates within our study. After completion of the task, participants completed the Borg Scale of Perceived Exertion to determine their subjective perception of level of exertion while playing Sudoku.

Paired Associate Learning Task

The PAL test was selected as this cued recall task is hippocampal dependent, while similar associative recognition tasks may not be (Caplan & Madan, 2016; Mayes, Montaldi, & Migo, 2007). One hundred and sixty words were selected for the PAL test from the Medical Research Council Psycholinguistic Database. Initially, 293 two-syllable words were selected that had an imageability score between 414–486 (Wilson, 1988). This range of imageability scores was selected to reduce variability in this factor, which can influence cued-recall accuracy (Paivio, 1969). Then, out of the semantically related words and words of the same root (i.e., working, worker, workhouse) all but one of which were removed, leaving 176 words. Eighty-eight word-pairs were then randomly constructed from this word pool using randomizer.org. The final eighty-word pairs were then randomly selected from the eighty-eight-word pairs and eight unique

lists of ten word-pairs were generated (Supplementary Table 2). Participants completed one PAL test in each of their 2 sessions; each PAL test comprised 4 different word-pair lists. The order of the word lists was randomized for each participant and no word pairs were repeated within or between the 2 sessions for a given participant.

For each PAL test, participants were presented with 4 lists of word pairs. The order of the word-pairs for each list was randomized for each participant. For a given list, participants were initially presented one word-pair at a time, centred side-by-side on a computer screen and were told to remember that those two words went together. Each pair was presented for 5 s with no delay between pairs, thus the 10 pairs were displayed over 50 s. This moderate presentation rate was selected to avoid floor and ceiling effects. After all the 10 pairs of a list were presented, a 30-second distractor task was administered, which involved counting backwards from a number selected randomly between 80 and 150, in steps of 7. The distractor task was used to minimize conscious or subconscious rehearsal of word pairs, to flatten a possible recency effect which can increase the recall of associations presented closest in time to the time of recall (Atkinson & Shiffrin, 1971; Koppenaal & Glanzer, 1990), and to increase the likelihood that the task was hippocampal-dependent (Caplan & Madan, 2016). Participants were then immediately given a printed page with the 10 left-side words from the previously presented word pairs of each list, with the second word of each pair absent and were given 1 min to write the corresponding missing words on the page. Participants repeated this procedure until they had completed all 4 lists for a given PAL test.

Analyses

Statistical analyses were performed using SPSS 23 software (IBM). Mean heart rates and the Borg Scale Ratings of Perceived Exertion scores were compared between the

exercise and control groups using separate independent-samples t-tests. To compare heart rates between groups, mean heart rates were averaged over the last 15 mins of the exercise and control tasks for each participant.

Performance on the PAL tests were scored as the percentage of correct responses on three lists from the first PAL test (baseline) and the four lists from the second PAL test. The first list from the first PAL test was not included in analyses to minimise the effect of task habituation on PAL test scores. Words with 1 spelling mistake were marked as correct, whereas words with 2 or more spelling mistakes were marked as incorrect. One blinded experimenter scored the data for each participant. For the statistical analyses, baseline scores were analysed to test for a sampling bias, using a 2x3 ANOVA with group (exercise, control) and Delay (2, 5, and 8 hrs) as between-subjects' factors. To compare the changes in PAL scores between sessions within experimental groups and between groups at comparable delays, a 2x2x3 repeated-measures ANOVA was performed, with time (baseline or post-intervention) as a within-subject's factor, and group (exercise or control) and delay (2, 5, or 8 h) as between-subjects' factors. Finally, to compare changes in PAL scores over time between the exercise and control groups, a 2x3 (group x delay) ANOVA was performed on the mean change in PAL scores between Session 1 and 2. When the ANOVAs identified significant main effects or interactions these were followed by simple effects (ANOVA) or paired-t-tests as appropriate. An alpha level of 0.05 was used to evaluate statistical significance. The Greenhouse-Geisser correction was applied to correct for violations of sphericity. Descriptive statistics are reported and are shown in the Figures as the mean $\pm$ one standard error, unless otherwise noted.

Results

Heart Rates and Perceived Exertion

Mean heart rates recorded before (time 0) and at the end of each minute of the exercise and control tasks are shown in Fig 2A. On average over the last 15 mins of the 2 tasks, participants in the exercise group had significantly higher mean heart rates (M=163.6 $\pm$ 1.6 beats per minute) than control participants (M=77.1 $\pm$ 1.4 beats per minute) [$F_{(1, 98)}$=15168, p<0.001]. Over that time, heart rates for participants in the exercise group were 82 ($\pm$ 0.7) % of their age-predicted maximum. Participants in the exercise group also had significantly higher ratings of perceived exertion than participants in the control group ($F_{(1, 100)}$=174.06, p<0.001), as shown in Fig 2B. Heart rates were not significantly different between the 3 control groups while they played Sudoku [$F_{(2, 51)}$=0.516, p=0.600] or between the 3 exercise groups while they ran on the treadmill [$F_{(2, 47)}$=0.599, p=0.554]. Mean heart rates for each of the control and exercise groups are shown in Supplementary Table 1B. Similarly, ratings of perceived exertion were not significantly different between the 3 control groups [$F_{(2, 51)}$=0.582, p=0.562] or the 3 exercise groups [$F_{(2, 49)}$=2.002, p=0.146].

Paired Associate Learning

Mean scores on the first PAL tests (baseline) for the control and exercise groups are shown by the grey bars in Figure 3A and B, respectively, with data from individual participants represented by the dots. These baseline scores did not differ across the six sub-groups as there were no significant main effects of group or delay and no significant interaction when only these data were included in the analysis (p>0.05). Overall, participants scored 41.4 $\pm$ 2.2% at baseline, indicating that on average they recalled approximately 4 of the 10-word pairs in each list. Scores on tests taken after

participants played Sudoku or ran on the treadmill are shown by the hatched bars in

Figure 3A and B, respectively. When these data were included in the analysis there was

a significant 3-way interaction between time, group and delay [$F_{(2, 100)}$=4.006, p=0.021].

Simple effects analyses, with a separate 2x2 ANOVAs at each delay, identified that

there was no main effect of time or group at after either 2 hrs delay [$F_{(1,34)}$=0.001,

p=0.980]; group [$F_{(1,34)}$=0.489, p=0.489]) or 5 hrs delay [$F_{(1,34)}$=0.009, p=0.924]; group

[$F_{(1,34)}$=2.133, p=0.153]). Furthermore, there was no significant interaction between

time and group after 2 [$F_{(1, 33)}$=2.369, p=0.133] or 5 hrs delay [$F_{(1,35)}$=1.934, p=0.173].

After 8 hrs delay there was also no main effect of time [$F_{(1,32)}$=3.242, p=0.081] or group

[$F_{(1,32)}$=0.658, p=0.423], however, the interaction between time and group was

significant [$F_{(1, 32)}$=5.824, p=0.022]. Post-hoc, paired-samples t-tests revealed that

scores on PAL tests that were performed 8 hrs after exercise (32.7 $\pm$ 5.6%) were

significantly lower than scores for the same individuals on tests taken at baseline (41.3

$\pm$ 5.5%; t(15)=2.547, p=0.022). By comparison, scores on PAL tests performed 8 hrs

after playing Sudoku (44.6 $\pm$ 6.7%) were not significantly different than scores at

baseline (43.3 $\pm$ 6.8%; t(17)= -0.519, p=0.611).

As a complementary approach, and as a way to normalise the data to each

participant's own baseline score, we subtracted the scores on the second PAL test from

the baseline test for each participant and these data are shown in Figure 4. When

analysed in this way there was a significant interaction between group and delay [$F_{(2, 100)}$

= 4.006, p = 0.021]. Post-hoc independent-samples t-tests showed that there was a

significant difference between exercise groups (-8.59 $\pm$ 3.3%) and control groups (1.25

$\pm$ 2.4%) after 8 hrs delay [t(32)=2.413, p=0.022], but not at the 2 [t(33)= -1.539,

p=0.133] or 5 hrs delay [t(35)= 1.391, p=0.173].

Eight hours after exercising participants performed 8.6% worse than they did on tests taken at baseline. Similarly, 8 hrs after exercising participants performed 9.8% worse than participants in the control group who had played Sudoku 8 hrs earlier. The effect size for the difference in the scores between the exercise groups at 8 hrs and baseline scores was small (Cohen's d=0.39). The effect size for the difference in the scores for the exercise group versus control group at 8 hrs was large (Cohen's d=0.82).

Discussion

The current study was designed to investigate the time-course of the effects of acute exercise on hippocampal-dependent associative memory over a longer time scale than had been tested previously. We found no effect of exercise on PAL test scores, our measure of associative memory, 2 or 5 hrs after exercise. Scores on PAL tests taken 8 hrs after exercise, however, fell significantly below scores on tests taken at baseline and scores for control participants. These results suggest that exercise can negatively influence the ability to encode and retrieve new information even hours after exercising.

Exercise Intensity

Mean heart rates of participants in the exercise group were 82% of their age-predicted maximums over the last 15 mins of the exercise bout, which corresponds to the upper limit of the range considered to be vigorous exercise by the Centers for Disease Control and Prevention (2015). The mean Borg scale rating of perceived exertion of 13, for the exercise group, falls in the middle of the range that represents moderate exercise (Centers for Disease Control and Prevention, 2015). Heart rates while control participants played Sudoku were relatively unchanged from baseline and their mean Borg scale rating of perceived exertion of 7 is between "no exertion at all" and "extremely light" (Centers for Disease Control and Prevention, 2015). Exercise

intensity, as measured by both heart rate and ratings of perceived exertion, did not vary across each delay time point within each of the groups. This suggests that each group did not have objective or subjective differences in level of exercise intensity that could explain the decrement in PAL test performance.

Time-Dependent Effects of Exercise on Associative Memory

It has been well-established that associative memory can be enhanced within ~1 hr after exercise (Coles & Tomporowski, 2008; Labban & Etnier, 2011; Winter et al., 2007) and one study (Basso et al. 2015) suggests that this effect may subside by 2 hrs. Presently, scores on PAL tests taken 2 or 5 hrs after running on a treadmill for 20 mins were not different from scores on tests taken before the exercise or scores from control participants. This suggests, in accordance with Basso et al. (2015), that exercise does not facilitate new associative memory formation or retrieval 2 hrs after exercise and extends this window to 5 hrs after the exercise bout. In the one previous study to show an improvement in associative memory 2 hrs after exercise, the memory task was in the visual domain (Bosch et al., 2017) and the exercise was performed 2 hrs after encoding and before retrieval. Thus, it was thought that acute exercise improved memory by enhancing consolidation between the encoding and retrieval of the memory task (Bosch et al., 2017). In another study, acute exercise improved hippocampal-dependent cued recall when the exercise was performed 4 hrs after encoding, and thus it was thought that the exercise improved the retention of memories (van Dongen et al., 2016). In contrast, in our study and that of Basso et al. (2015), verbal associative memory was assessed, and the exercise was performed before encoding the new information in the second PAL test. The discrepancies in the literature regarding the effects of acute exercise on different aspects of memory, many of which are hippocampal-dependent, reflect the different protocols used in the literature to assess memory. It also suggests

that acute exercise does not globally increase hippocampal function and rather increases specific hippocampal-dependent memory processes. The improvements in memory observed 2-4 hrs after exercise appear to be specific to the consolidation of already encoded memories (Bosch et al., 2017), or the strengthening of already existing memories (van Dongen et al., 2016), as the encoding or retrieval of new information over this interval is not influenced by exercise as shown by Basso et al. (2015) and the present study.

To our knowledge this is the first study to report an effect of acute exercise on human memory over such a long-time scale and is one of only a few to report an exercise-induced decrement in memory performance. When participants performed PAL tests 8 hrs after exercising, test scores were 8.6% and 9.8% lower than baseline and control scores, respectively. This corresponds to participants on average correctly recalling just over 4 word-pairs per 10 word-pair list before the exercise, to accurately recalling just over 3 word-pairs per list 8 hrs after exercise. In the two of the previous studies to report a negative impact of exercise on human memory, memory was tested immediately after a maximal treadmill exercise test (Covassin et al. 2007) or after participants ran a marathon (Eich and Metcalfe 2009). In both studies, the deficits in memory were attributed to excessive arousal and dehydration, factors that were unlikely to have contributed to the decline presently observed 8 hrs after running on a treadmill for 20 mins. It is plausible that the trajectory of post-exercise fatigue involves a depression of cognitive arousal and attention at 8 hrs after exercise, however there is currently no empirical evidence on the time course of post-exercise fatigue. Presently, although scores on PAL tests in the exercise group declined 8 hrs after exercise, scores for participants in the control group did not change over the same time period. Thus, circadian rhythms or the influence of activities of daily living are unlikely to account for

the presently observed declines in memory performance. Instead, given the close temporal proximity between encoding and retrieval in the current study (~2 min), we propose that the presently observed decrease in memory performance reflects the influence of exercise on the encoding and/or retrieval of new information, and it is independent of the influence of exercise on consolidation. Whether acute exercise also influences consolidation on such a long-time scale was not the focus of the present study and thus remains an open question.

Changes in memory function over such long-time scales may be due to transient changes in neurochemicals such as BDNF and glycogen, or processes such as LTP. For example, BDNF increases over the first 30 mins after exercise and decrease below baseline at 1, 2, and 3 hrs after exercise (Castellano & White, 2008; Yarrow et al., 2008), how BDNF changes at longer intervals is currently not clear. In addition, glycogen levels in the rat hippocampus peak approximately 6 hrs after exercise and remain above basal levels for 24 hrs (Matsui et al., 2012). Elevated glycogen and the resultant formation of lactate may enhance hippocampal-dependent memory processes through the astrocyte-neuron lactate shuttle (see Tsai, Chen, Calkins, Wu, & Kuo, 2016 for review). In humans, glycogen is known to be elevated in the brain after exercise, however, the time-course is unclear (Oz et al., 2009). The extent to which these changes in neurochemicals after acute exercise influence the encoding and retrieval of new human memories is not known. Finally, LTP is considered an underlying explanatory mechanism for the effects of acute exercise on memory (Loprinzi et al. 2019a). However, in our paradigm, the study-test delay was on the timescale of tens of seconds, too short for LTP. Although differences in early-phase LTP, and short-term plasticity processes, could play a role in our 8-h group's impairment effect, the time course of

acute exercise's influence on early-phase LTP and short-term plasticity processes is unknown.

Limitations and Future Directions

Participants in the current study were young adults. Thus, the present results may not generalize to other age groups as there is evidence that the way acute exercise influences cognitive processes can vary across the lifespan (Roig et al, 2013). The memory test used in the present study was the PAL test, an operationalization of associative memory in the verbal domain which is thought to be hippocampal-dependent (Caplan & Madan, 2016), thus the deficit in memory performance presently observed may be limited to this type of memory. Alternatively, the results may reflect a general decline in cognitive arousal and attention and are not specific to associative memory. Other limitations of the current study were that participants "self-selected" which subgroup they were in (i.e. 2, 5 or 8 hr delay) and we did not regulate participants' activities between the morning and afternoon sessions, both of which were requirements of our Human Research Ethics Board. However, participants had no knowledge of the experimental design when self-selecting delays, they were randomly assigned to a control or exercise group after self-selecting their delay group. Participants were excluded if they exercised between sessions, but we cannot rule out that uncontrolled factors including diet, napping, caffeine intake, and time spent in class influenced PAL scores in the exercise group. However, PAL scores for the control group did not change suggesting that changes in the exercise group were due to the exercise intervention. Finally, our measures of memory function were limited to 3 time points after exercise, and we did not correlate changes in memory performance with changes in neurochemicals known to be important for memory. Thus, we did not capture the true timing or amplitude of the peaks and troughs of the effect of exercise on

hippocampal-dependent memory processes nor did we shed light on the underlying processes that regulate this effect. Future research, in which memory performance is assessed with a greater temporal resolution in combination with biological assays will more accurately characterize the time-course and magnitude of the changes in associative memory after acute exercise provides clues about the underlying mechanisms. The results of such investigations will also be useful to inform practical applications of this work, for example, regarding timing of exercise programs or other vigorous activities to maximise, or at least not negatively impact, memory performance. We recommend that if people wish to augment the encoding and/or retrieval of new hippocampal-dependent associative memory they perform cardiovascular exercise in close proximity (~1 hr) to the memory task. Additionally, they should avoid tasks critically dependent on the formation of new associative memories around 8 hrs after exercising, to avoid impairments in performance. A challenge for future research in this area is that a comprehensive understanding of the influence of exercise on memory will require a systematic exploration of the time-dependent interaction between exercise and the vast array of processes involved in human memory.

Conclusions

A single bout of exercise has no effect on associative memory when encoding and retrieval of the new information are performed 2 or 5 hrs after the exercise. However, exercise has a negative effect on associative memory when encoding and retrieval are performed 8 hrs after exercising. These results suggest that the previously-reported benefits of exercise on memory are short-lived, and that time course of the effects of exercise on associative memory, and all aspects of memory, should be a

consideration when considering the timing of exercise programs and other vigorous activities in order to enhance, and not hinder, learning.

Acknowledgements

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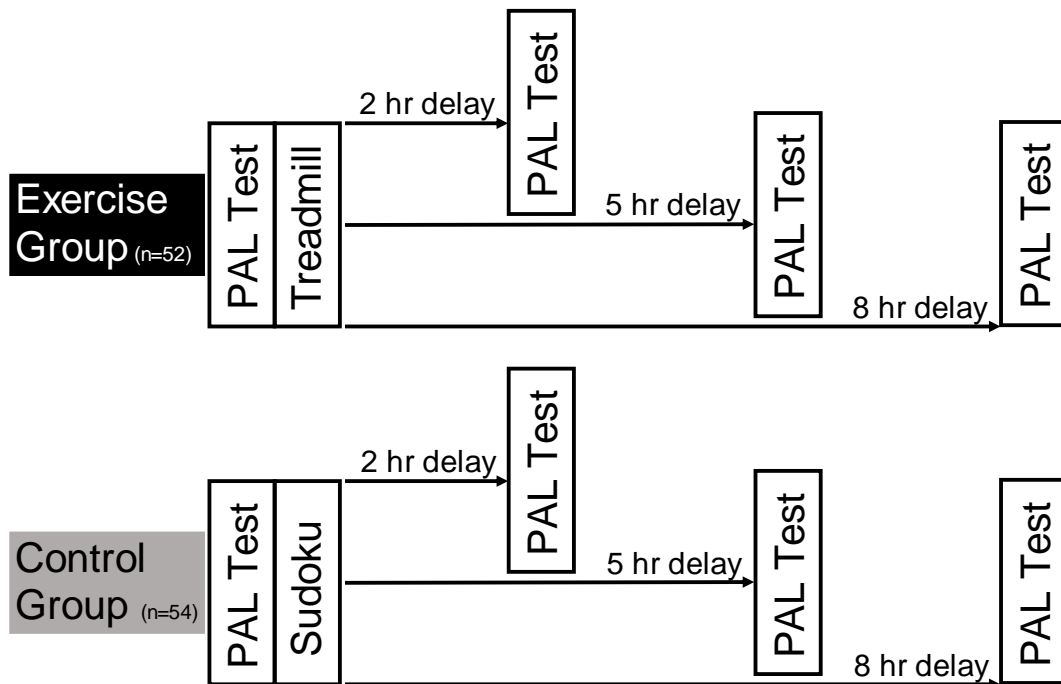   factor (BDNF). *Neuroscience Letters*, 479(2), 161-165.

Figures

Figure 1. Overview of the experimental design. Participants were divided into either an exercise or control group. In session 1, participants performed a baseline PAL test and then either ran on a treadmill (Exercise Group) or completed Sudoku puzzles (Control Group). For session 2, participants returned either 2, 5 or 8 hrs later to complete a second PAL test that was different than the first.
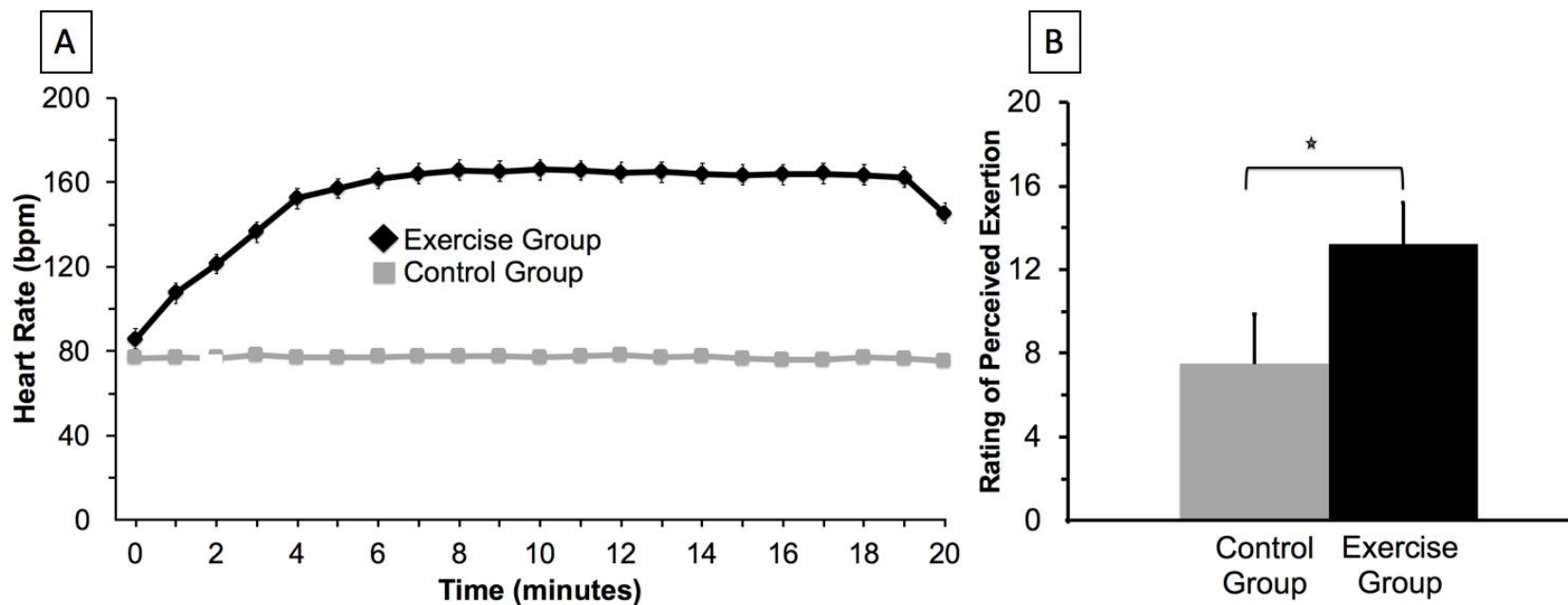
Figure 2. Mean heart rates and ratings of perceived exertion for exercise and control groups. Panel A shows the mean heart rates of participants in the exercise (black line) and control groups (grey line) recorded before (time 0) and at each minute throughout their respective tasks. Panel B shows the mean ratings of perceived exertion as measured using the Borg scale, where 6 represents minimal exertion and 20 represents maximal exertion, for participants in the exercise (black) and control (grey) groups.
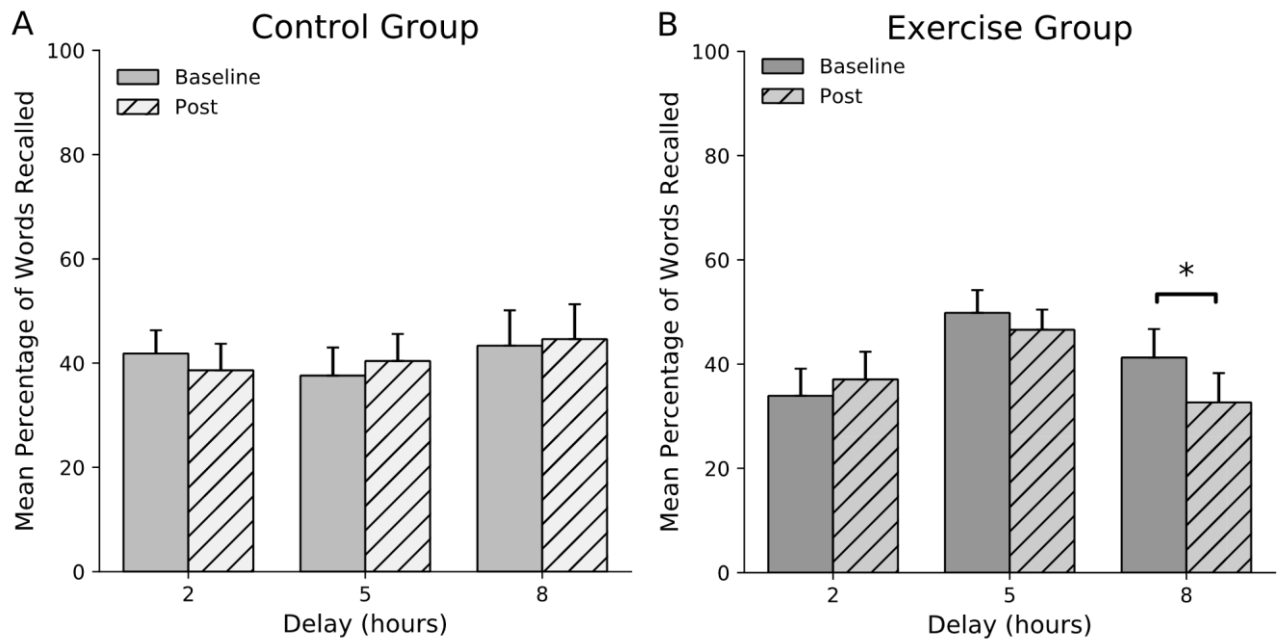
Figure 3. Scores on PAL tests for participants in the control (Panel A) and exercise (Panel B) groups. Scores represent the mean percentage of words recalled on tests taken before (Baseline) or at various delays after (Post) playing Sudoku (Panel A) or running on a treadmill (Panel B). Dots represent data from individual participants. Bars represent mean data for the group (+1SE). Asterisks represent significant difference between Baseline and Post scores ($P < 0.05$).
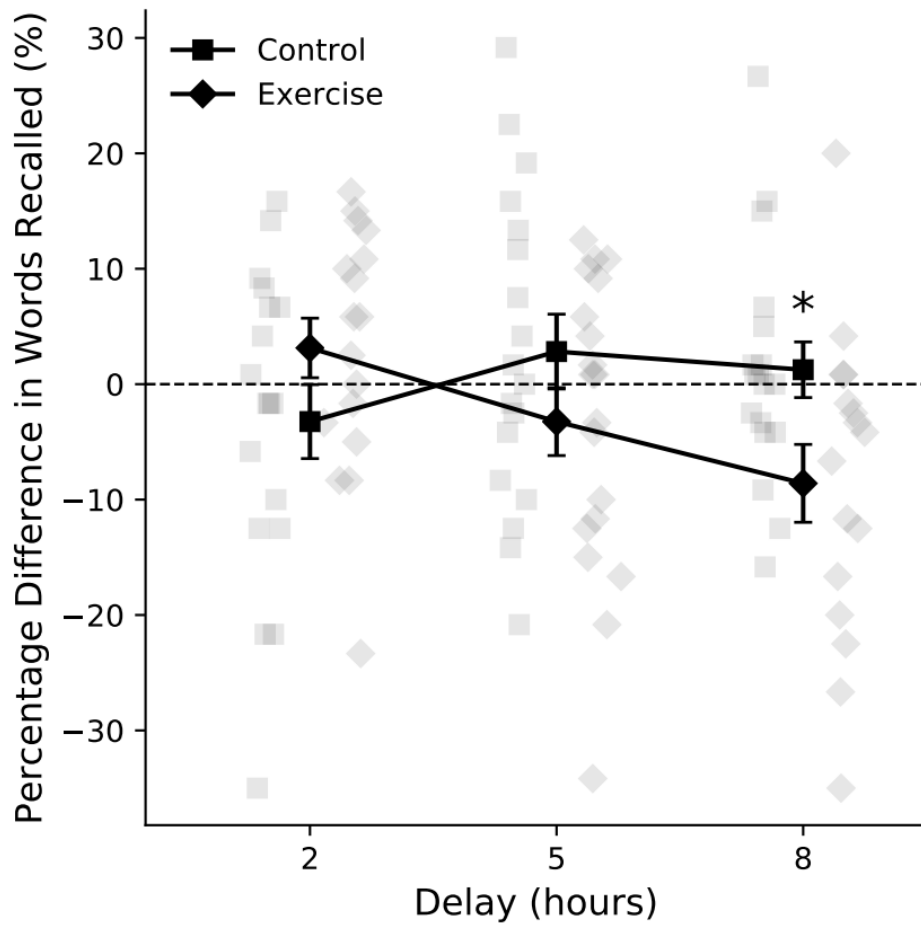
Figure 4. Scores achieved on the second PAL test reported as a percent change from

scores on tests taken at baseline. The diamonds represent mean data for the exercise

group and the square symbols represent mean data for the control group. Error bars

depict ± one standard error. Light grey squares represent data from individual

participants in the control group and light grey diamonds represent data from

individuals in the exercise group.