Does cardio-respiratory fitness protect memory from sleep deprivation?

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ABSTRACT

Introduction: Animal studies have demonstrated that physical exercise can protect memory from the effects of sleep deprivation (SD). We examined whether having a high cardio-respiratory fitness (VO_{2peak}) is associated with an enhanced capacity to encode episodic memory after one night of SD. Methods: Twenty-nine healthy young participants were allocated into either a SD group (N=19) that underwent 30 hours of uninterrupted wakefulness, or a sleep control (SC) group (N=10) that followed a regular sleep routine. Following either the SD or SC period, participants were asked to view 150 images as the encoding part of the episodic memory task. Ninety-six hours after viewing the images, participants returned to the laboratory to perform the recognition part of the episodic memory task, which required the visual discrimination of the 150 images previously presented from 75 new images introduced as distractors. Cardio-respiratory fitness (VO_{2peak}) was assessed with a bike ergometer graded exercise test. Group differences in memory performance were assessed with independent t-tests and associations between VO_{2peak} and memory with multiple linear regression. Results: The SD group showed a significant increase in subjective fatigue (MD[SE]=38.94[8.82]; p=0.0001), and a worse capacity to identify the original 150 images (MD[SE]=-0.18[0.06]; p=0.005) and discriminate them from distractors (MD[SE]=-0.78[0.21] p=0.001). When adjusted for fatigue, higher VO_{2peak} was significantly associated with better memory scores in the SD (R^2=0.41; β[SE]=0.03[0.01]; p=0.015) but not in the SC group (R^2=0.23; β[SE]=0.02[0.03]; p=0.408). Conclusion: These results confirm that SD prior to encoding impairs the capacity to create robust episodic memories and provide preliminary support to the hypothesis that maintaining high levels of cardio-respiratory fitness could have a protective effect against the disruptive effects of sleep loss on memory.
Keywords: Maximal Oxygen; Consumption; Sleep Loss; Insomnia; Physical Activity; Cognition.
INTRODUCTION

Sleep is essential to maintain neuroplasticity and optimize different aspects of cognition, including memory (1, 2). Memory is one of the aspects of cognition most sensitive to the effects of sleep loss (3). Even short periods of sleep deprivation (SD) can impair our capacity for both encoding and consolidating the information that we acquire during the day and thus our capacity to form strong memories (4). Animal and human studies have demonstrated that the impairments in memory that result from partial or total periods of SD are associated with impairments in neuroplasticity triggered by the effects of sleep loss (4). Interventions with the capacity to strengthen neuroplasticity such as physical exercise (5) could potentially protect memory against the effects of SD (6).

The use of physical exercise as a countermeasure to protect memory against the effects of sleep loss has been explored mostly in animal studies. Taken together, the results of these studies indicate that exposing rodents to cardiovascular training for 4-6 weeks can protect memory from an acute episode (12-96 hours) of SD (6). Importantly, the protective effect of exercise was observable using different memory tasks, suggesting that the effect could be generalizable to different types of memory. Furthermore, some of these animal studies demonstrated that cardiovascular training preserved mechanisms involved in memory formation processes such as hippocampal long-term potentiation from the deleterious effects of SD. These findings reinforce the idea that the protective effect of exercise on memory against sleep loss could involve neuroplasticity mechanisms (6).

Only two human studies have investigated the protective effect of exercise on memory against the effect of SD (7, 8). In one study, participants were randomized into either a control group or a group that exercised 15 min at moderate intensity. Following 24 hours of sustained wakefulness, memory was assessed prior to and after either the control or the exercise intervention. Exercise did not produce any benefit on memory, but since the SD protocol did
not cause any memory impairment, the potential protective effect could not be assessed. In another study (7), the impact of a 40-hour SD protocol on different aspects of cognition was assessed after seven weeks of moderate to high intensity cardiovascular training performed three times per week. Training did not reduce the degradation of working memory that was observed after SD, suggesting that the protective effect reported in animal studies cannot be extrapolated to humans. However, since working memory is considered more an aspect of executive function than a memory function per se (9), more studies are needed to confirm if physical exercise could confer protection against the effects of SD on other types of memory such as episodic memory (6).

The maximal oxygen consumption (VO_{2peak}) achieved during a graded exercise test is considered the gold standard measure of cardio-respiratory fitness (10). In short, the level of cardio-respiratory fitness depends on the capacity of our heart to send oxygenated blood to exercising muscles (i.e., stroke volume x heart rate) and the capacity of our muscles to utilize oxygen (i.e., arteriovenous O_2 difference). Although heritability factors modulate the response to exercise for improving cardio-respiratory fitness (11), individuals who have higher levels of physical activity tend to achieve higher VO_{2peak} values in maximal graded exercise tests, which are the gold standard measure to assess cardio-respiratory fitness. Higher levels of cardio-respiratory fitness, in turn, also tend to be associated with enhanced neuroplasticity (5) and memory performance (12). Hence, maintaining a high VO_{2peak} could potentially protect memory against the effects of SD (6).

Cardio-respiratory fitness has been shown to moderate the deleterious effects of poor sleep on episodic memory in older adults (13). However, whether having a high VO_{2peak} capacity can protect episodic memory encoding against the effects of SD is not known. This study investigated whether having a high cardio-respiratory fitness (VO_{2peak}) is associated with an enhanced capacity to encode episodic memory against the effects of a full night of SD. The
study included one SD group that underwent 30 hours of uninterrupted wakefulness and a sleep control (SC) group that followed a normal sleep routine. We hypothesized that SD would impair the capacity to encode episodic memory (14), but that this impairment would be attenuated in those participants with higher cardio-respiratory fitness, who will be less susceptible to the negative effects of SD.

METHODS

Participants

Participants were recruited using advertisements posted on social media and email lists from McGill university (Montreal, Canada). They were included if they were: 1) aged between 18 to 35; 2) without any history of neurological or psychiatric clinical conditions; 3) without any contraindication to perform cardiovascular exercise; 4) without any previous history of sleep disorders; 5) not currently taking medications or recreational drugs (e.g., cannabis) affecting the nervous system (e.g., anti-depressants); 6) sleeping more than six hours per night and following a regular sleep routine (i.e., going to bed between 9 pm and 12 am and waking up between 6 am and 10 am).

Participants were excluded if they: 1) worked nightshifts; 2) had been on a transmeridian flight crossing three time zones or more during the month prior to participation in the study; 3) were consuming more than three stimulants a day (e.g., coffee, tea, energy drinks); 4) used any medication to improve sleep, including melatonin or other over the counter alternatives (e.g., antihistaminic). The protocol was approved by the local Ethics Research Board (CRIR-1507-1220) and all participants provided written consent before taking part in the study. A compensation of $125 was provided to cover for transportation and/or parking expenses.
Sample size estimation

The required sample size was estimated from a previous study that used the same episodic memory paradigm and a similar SD protocol to disrupt memory encoding (14). The effect size value of that study, calculated from the subtraction of mean differences in memory between the SD group and the SC group, was 3.01 (15). Using a more conservative effect size of 1.5 and an allocation ratio of 2:1 to increase the power of the SD group to be able to explore associations between cardio-respiratory fitness and memory, we estimated that we would need 20 participants in the SD group and 10 participants in the SC group to detect significant differences ($\alpha=0.05$) in episodic memory performance ($d'$) with a power ($1-\beta$ err prob) of 0.95.

We did not have previous data to estimate the sample size for the association between cardio-respiratory fitness and memory in the SD group precisely, but we anticipated that 20 participants would provide reasonable power (>85%).

Design

The study, which used a between-subject controlled design with two experimental groups, comprised one pre-screening visit that was performed remotely due to COVID-19, and, depending on the allocation group, two (SD) or three (SC) in-person laboratory visits (Figure 1). The SC group required three laboratory visits instead of two because, unlike the SD group, they did not stay in the laboratory for the SD protocol and therefore had to come back for one additional visit to perform the encoding part of the memory task. Participants were instructed to avoid vigorous physical activity 24 hours prior to each in-person visit to reduce the potential confounding effects of acute exercise on memory (16).

Procedures

The pre-screening visit, which was conducted electronically six days before the first in-person visit, was identical for both groups. Participants received a package by email that
included the consent form as well as sleep quality and physical activity-related questionnaires, which had to be filled out and emailed back to the researchers before the first in-person visit. The electronic package also included a sleep diary that participants needed to fill out every day until the first in-person visit. The sleep diary confirmed that a regular sleep routine was followed and thus that participants were eligible to start the experiments in the laboratory. If the diary showed an irregular sleep routine, participants were afforded three additional days to obtain a regular sleep schedule before proceeding to the first in-person visit.

SD group

Participants in the SD group reported to the laboratory six days after the screening visit for the first in-person visit (Figure 1). Upon arrival (~6 pm), they were outfitted with an actigraphy monitor used to record their sleep-wake cycles until the end of the study. They were then exposed to a standardized SD protocol, completing a total of 30 hours of sustained wakefulness counted from their wake-up time. Fatigue and alertness were assessed upon arrival and immediately before the encoding part of the episodic memory task. After 30 hrs of wakefulness, participants performed the encoding part of the episodic memory task. After encoding, they were provided with a new sleep diary, which had to be filled out daily until the second in-person visit.

Ninety-six hours after the end of the first in-person visit, participants reported to the laboratory for the second in-person visit. Upon arrival, they returned the actigraphy monitor and sleep diary. Then, participants performed the same test of alertness that they performed before encoding, followed by the recognition part of the episodic memory task. After performing the recognition task, they completed a cognitive battery, followed by a graded exercise test to assess their cardio-respiratory fitness level (VO2peak). Note that, because of COVID-19 restrictions, the cognitive tests and graded exercise test were done during this visit instead of the pre-screening visit to limit the number of visits to the laboratory.
Like the SD group, participants in the SC group also reported to the laboratory six days after the screening visit for the first in-person visit (Figure 1). However, after the first visit, they returned to their home to follow their normal sleep routine. The second in-person visit of the SC group took place 30 hours after the wake-up time of the day on which they had their first laboratory visit, therefore matching the 30 hours of sustained wakefulness undergone by the SD group. Upon arrival to the laboratory, participants performed the tests of fatigue and alertness followed by the encoding part of the episodic memory task. The third in-person visit of this group was identical to the second in-person visit described for the SD group (Figure 1).

SD protocol

We used a standardized SD protocol that we have used in previous studies (17, 18). In short, participants followed a structured activity schedule to minimize the discomfort related to extended wakefulness while controlling for potential confounders (e.g., changes in arousal level and physical activity) (14). During the SD protocol, participants were limited to internet use, email, reading, as well as board and card games. A standardized walking activity regime that involved five minutes of walking every hour was also implemented. To ensure compliance, the time spent in all these different activities was recorded using a diary log and participants were monitored by one of the investigators who accompanied them all the time.

Assessments

Sleep quality and physical activity

The Pittsburgh Sleep Quality-Index (PSQI) (19), the Epworth Sleepiness Scale (ESS) (20), and the International Physical Activity Questionnaire (IPA-Q) long-form (21) were used to assess sleep quality and physical activity level, respectively. The PSQI is a 19-item questionnaire to assess sleep quality over a 30-day reference period that has seven components.
(19). Each component is scored from 0 (no difficulty) to 3 (severe difficulty). The scores are summed to produce a total score ranging from 0 to 21, with higher scores indicating worse sleep quality, and >5 usually used as cut-off to indicate sleep problems. The ESS is a questionnaire to assess daytime sleepiness, in which participants rate their chance of dozing off in eight different situations to obtain a global score of sleepiness (20). The total score ranges from 0 to 24, with >10 being used as cut-off for significant sleepiness. The IPA-Q is a questionnaire that, using a seven-day reference period, assesses physical activity in different areas such as work, leisure time, transportation, gardening/yard work and household chores (21). To estimate energy expenditure, the global physical activity score was converted into metabolic equivalents (METs) (21).

Sleep-wake cycles

Sleep-wake cycles were assessed using sleep diaries and actigraphy monitors (22). In the sleep diary, participants annotated the time that they went to bed and the time they woke up as well as other sleep-related relevant information (e.g., time to fall sleep, number of times and reason why they interrupted their sleep). The first sleep diary was used to ensure that participants followed a regular sleep routine prior to the first in-person visit and the second sleep diary was used to confirm that the bed and wake up times annotated by the participant coincided with the sleep and wake up periods marked by the actigraphy monitor.

Actigraphy data were collected with the Actiwatch 2® monitor (Respironics, Philips), which has shown good validity to measure sleep when compared against polysomnography (23). Participants wore the actigraphy monitor on their non-dominant wrist from the first to the last in-person visit. Data extracted included activity counts, a surrogate of physical activity (24), as well as measures of sleep such as total sleep time, sleep onset latency, sleep efficiency, and wakefulness after sleep onset (25). Actigraphy data, acquired using 60-second epochs and
an activity threshold of 40 counts, allowed us to investigate differences in sleep-wake patterns between groups both before and after the encoding part of the episodic memory task. Monitoring sleep patterns after encoding was important to determine if by recovering sleep during memory consolidation could rescue memory in the SD group.

Fatigue and alertness

To assess fatigue severity, we used an adapted version of a visual analog scale, which has been shown to have excellent psychometric characteristics (26). Fatigue levels ranged from minimal (0) to maximal (100), with higher scores representing greater fatigue. Alertness was measured on an electronic tablet (SM-T280, Samsung) with the Sleep-2-Peak® application, which has been validated against psychomotor vigilance tests for monitoring alertness change due to sleepiness and fatigue during SD (27). This application requires participants to tap the tablet screen with the index finger in response to a visual stimulus presented at random intervals for three minutes. The average reaction time calculated over 10 trials was recorded and used as a surrogate of alertness (27).

Cognitive status

Cognitive function was assessed with a test battery built with the Psychology Experiment Building Language software (PEBL; http://pebl.sourceforge.net). The following cognitive functions were assessed: stimulus inhibition, spatial episodic memory, working memory, executive function, and processing speed. To this end, the following cognitive tests were used: Flanker (28), Buildup (29), Corsi (30), Stroop Colour (31), and Pattern Comparison (32). The battery was performed in front of a 23” computer screen and participants responses were recorded with a keyboard (Business Multimedia Keyboard KB522, Dell). A composite score calculated from the t-scores of each cognitive task summed using equal weightage was used as global score of cognitive function (33).
Cardio-respiratory fitness

Cardio-respiratory fitness was assessed with a bike ergometer (Corival®, Lode) graded exercise test, which we have used in previous studies (34, 35). The test started with a 3 min of warm-up at a resistance of 50W and intensity was then increased every minute by 10-20W depending on the physical activity level of the participant (10). Participants were asked to maintain a pedalling rate above 60 rpm. Heart rate (H7®, Polar) and rate of perceived exertion (6-20 Borg Scale)(36) were collected at baseline, at the end of the warm-up period, at the end of each one minute-block, and at the end of the test. Blood pressure was collected at baseline and at the end of the test using an electronic stress test monitor (Tango 2®, SunTech Medical). An online gas analysis system (Vmax Encore 29C®, Carefusion) recorded O₂ consumption and CO₂ exhalation. Exercise was stopped when participants could not continue pedalling at 60 rpm for five seconds or when they reached volitional exhaustion. The highest VO₂ value achieved during the last stage of the test was used to determine the cardio-respiratory fitness level (VO₂peak) (37).

Episodic memory

We used an episodic memory task that has shown to be sensitive to the effects of SD prior to encoding (14). During encoding, participants were shown 150 neutral images from the International Affective Picture System, subdivided into 5 blocks of 30 images, with 30 seconds of rest in between blocks. All participants viewed the same images, but the order of appearance was randomized among participants and counterbalanced between groups so that the same proportion of participants in each group saw the same image sequence. Images included non-renowned people, landscapes, scenes, and objects. Each trial started with a fixation crosshair (2000 ms), after which participants had 3000 ms to view the image and rate their level of arousal from 1 (no arousal) to 4 (maximal arousal) by pressing a keypad button (RB-740,
The arousal assessment was used to confirm that participants had seen the image and remained awake during encoding. If no response was obtained, the trial was marked as omitted.

During the recognition part of the memory task, participants were shown the same 150 original images that were displayed at encoding intermixed with 75 new neutral images that were introduced randomly as distractors (14). Like with the encoding part of the memory task, each trial of the recognition task started with a fixation crosshair (2000 ms), after which participants had 3000 ms to view the image and respond if they had seen the image on the previous visit or not using a keypad button (RB-740, Cedrus). Like with encoding, images during recognition were also randomized and counterbalanced among participants. Both encoding and recognition were designed with the software Superlab 6 (Cedrus).

The recognition task resulted in one of these four different memory outcomes: original image correctly identified (hits), original image incorrectly identified (misses), distractor correctly identified (correct rejections), and distractor incorrectly identified (false alarms). Using these four outcomes we calculated the hit (hits/original images) and false alarm (false alarms/distractors) rates (14). The primary outcome of memory performance was the capacity to discriminate between original images and distractors, which was calculated with a discrimination index (d’) obtained by subtracting the z scores of the false alarm rate from the z scores of the hit rate (39).

**Statistical analyses**

Analyses were carried out with SPSS 29®. Using histograms and normal quantile plots, data were first plotted to visualize variable distributions for each of the two groups separately. The Shapiro-Wilk’s test was used to confirm normality. Differences in demographic variables between groups were explored with independent t-tests or Wilcoxon rank sum tests for continuous variables and Chi-square tests for categorical variables. Independent t-tests or
Wilcoxon rank sum tests were used to determine differences between groups for measures of fatigue, alertness, sleep, and episodic memory. The results of between groups comparisons are reported as mean differences (MD) and standard errors (SE). Cohen’s (d) effect sizes were calculated for the comparisons of all memory outcomes between groups. To minimize the potential impact of differences in attention between groups on memory, images whose responses were omitted at encoding (0.67% of images viewed by all participants) were removed from the analyses.

Associations between memory performance (d’) and cardio-respiratory fitness (VO_{2peak}) were assessed independently for each group with least-squares multiple regression analyses. To control for the effects of fatigue on memory, the regression model included changes in fatigue during the SD and SC as covariates. Cook’s distance values were used to determine the influence of extreme observations on the regression model. All analyses were performed with 2-tailed probability tests with the statistical level (α) set at 0.05. Unless otherwise stated, data are presented as means and standard deviations (SD).

RESULTS

Thirty-one participants were recruited but the cardio-respiratory fitness data of one participant in the SD group could not be collected because of technical problems during the graded exercise test and another participant in the SC group did not comply with the experimental protocol and left the study before completion. Since the data from these two participants could not be included, they were removed from the study. Nineteen participants were allocated in the SD group and 10 in the SC group (Table 1). The two groups were similar in terms of age, biological sex, as well cardiorespiratory fitness (VO_{2peak}) and cognitive status. Similarly, no significant differences in self-reported sleep quality and physical activity level between groups prior to participation in the study were observed. Importantly, VO_{2peak} was
significantly correlated ($R^2=0.263; \ p=0.006$) with physical activity, confirming that VO$_{2\text{peak}}$ is a valid surrogate measure of the level of physical activity.

The first sleep diary data showed that, during the five days prior to the first in-person visit, all participants followed a regular sleep routine that was similar between groups. During this period, on average, the SD group slept 7 hours and 29 minutes each night while the SC group slept 7 hours and 54 minutes each night ($p=0.20$). The average number of sleep interruptions per night recorded during this period was also very similar between groups ($p=0.73$), with the SD and SC groups reporting, on average, 0.79(0.62) and 0.70(0.70) interruptions per night, respectively.

The baseline levels of fatigue (MD[SE]=−7.16[8.02]; $p=0.38$) and alertness (MD[SE]=1.06[19.67]; $p=0.95$), assessed as reaction time upon arrival on the first in-person visit, were not significantly different between groups. In contrast, fatigue assessed immediately before the encoding part of the memory task was worse (MD[SE]=31.78[8.81]; $p=0.0001$) in the SD (60.68[6.00]) than in the SC group (28.90[3.92]). Differences between groups in the deterioration of fatigue during the SD and SC periods were also statistically significant (MD[SE]=38.94[8.83]; $p<0.0001$) but changes in alertness were not (MD[SE]=−4.44[11.44]; $p=0.70$).

Table 2 provides details on the behavioral responses of the two groups while performing the encoding and recognition parts of the episodic memory task. At encoding, there were no significant differences between groups in the number of responses omitted (MD[SE]=0.20[1.02]; $p=0.07$), response time to rate arousal (MD[SE]=51.70[113.21] $p=0.65$), or arousal ratings (MD[SE]=0.013[0.14]; $p=0.92$). Similarly, no significant differences were observed between groups in the number of responses omitted (MD[SE]=0.26[0.62]; $p=0.33$) and the
overall response time ($\text{MD[SE]}=0.07[64.56]; p=0.99$) during the recognition task. The
response time for trials marked as hits ($\text{MD[SE]}=52.94[54.78]; p=0.34$), misses ($\text{MD[SE]}=-78.30[69.11]; p=0.30$), correct rejections ($\text{MD[SE]}=40.82[70.67]; p=0.57$), and false alarms ($\text{MD[SE]}=-15.17[95.23]; p=0.87$) during the recognition task were not significantly different between groups.

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The results of the analyses pertaining to the comparisons of memory outcomes between groups are shown in Figure 2A-C. Exposure to the SD protocol appeared to have a significant impact on the capacity of individuals to effectively encode episodic information. Overall, the SD group showed worse hit rates (Figure 2A) and false alarm rates (Figure 2B) than the SC group. However, only the hit rate ($\text{MD[SE]}=-0.18[0.06]; p=0.005; d=1.20$), and not the false alarm rate ($\text{MD[SE]}=-0.05[0.04]; p=0.19; d=0.52$), was significantly worse in the SD group. More importantly, the primary memory outcome, which was defined as the capacity to correctly discriminate between the 150 original images and the 75 distractors ($d'$), was significantly poorer in the SD than in the SC group ((MD[SE]=-0.78[0.21] p=0.001; d=1.44) (Figure 2C).

------INSERT FIGURE 2 HERE------

The tabulated results of the regression analysis are reported in Table 3. The SC group showed no significant associations ($R^2=0.23; F_{2,7}=1.02; p=0.408$) between cardio-respiratory fitness and memory performance (Figure 3B). In contrast, a significant association was found in the SD group, with cardio-respiratory fitness explaining 41% of the variance in episodic memory performance ($R^2=0.41; F_{2,16}=5.51 p=0.015$) (Figure 3A). Participants exposed to the SD who achieved higher levels of $\text{VO}_{2\text{peak}}$ in the graded exercise test were less impacted by the effects of sleep loss on the encoding of episodic memory. Importantly, the association between episodic memory performance and cardio-respiratory fitness ($\text{VO}_{2\text{peak}}$) in the SD group was
significant (p=0.0258), even if fatigue was not entered in the model as covariate. Furthermore, the deterioration of reaction times in the SD group was not correlated (p<0.05) with any of the memory outcomes (hit and false alarm rates and discrimination index) or with VO\textsubscript{2peak}, suggesting that the association between episodic memory performance and cardio-respiratory fitness (VO\textsubscript{2peak}) was not influenced by changes in alertness.

The actigraphy and second sleep diary data revealed differences between groups in the sleep-wake cycles assessed immediately after encoding. Specifically, 16 participants in the SD group took a day-time nap (224.81[85.91] minutes) after the encoding session while neither participant in the SC group napped. Furthermore, nap sleep efficiency in the SD group was very high (91.72% [5.78]). The days that followed the first night after encoding participants returned progressively to their regular activity patterns. Daily average activity counts were similar between the SD (289.85[71.98]) and SC (314.97[74.66]) groups (MD[SE]=-25.12[30.92]; p=0.44), suggesting no remarkable differences in physical activity patterns post-encoding.

Detailed information about the sleep measures collected with actigraphy during the four nights that followed encoding and preceded recognition are shown in Table 4. On average, there were no differences between groups in sleep measures during the four nights post-encoding. However, the night following the encoding session, participants in the SD group slept longer (MD[SE]=2.23[0.52]; p<0.001) and more efficiently (MD[SE]=5.40[1.71]; p=0.005) than the SC group. This result suggests that sleep overcompensation during consolidation cannot rescue memory from poor encoding. Importantly, the night preceding the recognition task, sleep duration (MD[SE]=0.15[0.38]; p=0.995), sleep onset latency
(MD[SE]=−0.17[5.24]; p=0.350) and sleep efficiency (MD[SE]; 5.23[3.32]; p=0.238) were not significantly different between groups.

**DISCUSSION**

This study confirms previous investigations demonstrating that, besides its critical role in memory consolidation (40), sleep is also essential for successful episodic memory encoding (14). Yoo et al., were the first to report that 35 hours of extended wakefulness that involved one full night of SD prior to encoding had a deleterious effect on episodic memory that was associated with impairments in brain activity and connectivity during the encoding part of the memory task (14). We cannot discard that in our study the SD protocol did not affect early consolidation processes post memory encoding (41). However, it should be noted that participants in the SD group showed poorer memory performance than the SC group despite taking a daytime nap, sleeping more hours, and showing higher sleep efficiency the night of sleep that followed the SD protocol. Hence, increasing sleep quantity and efficiency during consolidation was not enough to compensate for the sleep debt accumulated during SD and, more importantly, to rescue the memory from a suboptimal encoding process (14).

The exact mechanisms explaining why sleep loss prior to memory encoding impairs episodic memory remain to be determined (3). Animal studies have shown that SD impairs the capacity to induce long-term potentiation in the hippocampus during encoding and reduces the availability of signalling proteins involved in memory processing (4), with adenosine accumulation during extended wakefulness possibly playing an important role (42). Studies in humans have also shown that SD impairs hippocampal activation, producing compensatory alterations in the connectivity of brain networks involved in attentional processes during the encoding of episodic memory (14). These compensatory mechanisms could be due, at least in part, to a disruptive effect of SD on synaptic homeostasis before encoding (43). Certainly, sleep prior to encoding has shown to be essential in restoring the synaptic strength of previously
activated neurons, re-establishing their capacity to form new synapses, and thus preparing them to encode new information again (44).

Our study revealed a significant association between VO\textsubscript{2peak} and episodic memory in the SD group. This novel finding supports the hypothesis that maintaining an optimal cardio-respiratory fitness level could have a protective effect on memory against the effects of a single bout of SD (6). Importantly, this association was independent of the behavioral responses of participants during encoding (e.g., number of omitted responses, response times, arousal ratings), which were similar in both groups (Table 2). Unlike changes in fatigue, alertness deterioration was not entered in the regression model because it was not significantly different between groups, and it was not associated with any memory outcome. The lack of differences between groups in alertness was unexpected because the Sleep-2-Peak® application has shown good sensitivity to detect changes in alertness during SD (27). It is possible that taking more baseline measures to minimize any potential learning effect over multiple assessments could have increased the sensitivity of this measure. Taken together, our results suggest that the protective effect of VO\textsubscript{2peak} on memory encoding against SD cannot be exclusively attributed to an enhanced capacity of the more fit individuals to endure the effects of sleep loss on fatigue and alertness.

The protective effect of VO\textsubscript{2peak} on memory against SD could be explained, at least in part, by an enhanced neuroplasticity of the individuals with a higher cardio-respiratory fitness level (6). Indeed, there is evidence that people with a higher cardio-respiratory fitness have a more resilient brain with a greater cognitive reserve (45) that could potentially make them less susceptible to the effects of SD on memory (13). This hypothesis is consistent with emerging mechanistic evidence from animal studies demonstrating that cardiovascular training protects hippocampal neuroplasticity and memory from the deleterious effects of SD (6). Whether the findings of these animal studies can be extrapolated to humans, however, is still to be
elucidated. More mechanistic studies exploring how exercise changes the structures and functions of the human brain regulating the sleep-wake cycle (46), and how exercise-induced neuroplasticity adaptations in structures such as the hippocampus (47) might protect different stages of the episodic memory formation process from the effects of sleep loss are clearly needed (6).

LIMITATIONS

This study has limitations that need to be acknowledged. Firstly, groups were not randomized into the different interventions. Instead, we tested first the participants of the SD group and compared their memory scores with the scores of a previous study using the same SD paradigm (14). This preliminary step was important because previous exercise studies have failed to validate if the SD protocol used was taxing enough to disrupt memory (8). Starting with the SD group also allowed us to obtain preliminary data to evaluate if obtaining the sample size needed to detect associations between memory scores and CRF was realistic. Once we confirmed that the SD paradigm disrupted memory, we added the SC group as comparison. The fact that both groups had similar characteristics (Table 1) suggests that the findings of the study cannot be attributed to lack of randomization.

Secondly, since the study was designed to limit in-person visits, the first visit was performed remotely and not in-person, which limited our capacity to give participants an actigraphy monitor to objectively assess their sleep-wake cycles prior to the first in-person visit. To circumvent this limitation, we used sleep diaries that have been validated to monitor sleep-wake cycles (48). Secondly, the SC group was introduced as comparison with the SD group to confirm that the SD protocol disrupted memory. However, this group was not powered to detect associations between cardio-respiratory fitness and memory performance (49). While the small number of observations in the SC group could have contributed to the lack of
assocation between VO2peak and memory, it should be noted that the association between cardio-respiratory fitness (VO2peak) and memory is complex and does not always follow a linear pattern(50).

Another limitation of the study refers to the power of the regression analysis and the low number of males in the study. When we designed the study, we had no previous data to estimate the sample size required for the regression analysis. We used the data from Yoo et al. (14) to ensure that our study was powered enough to detect differences between groups in memory as this has been a common problem in previous exercise studies, whose SD paradigms have failed to impair memory (8). We also used a 2:1 group allocation ratio to increase the number of participants in the SD group to explore associations with increased power. Our sample size estimation was appropriate to detect differences between groups in episodic memory and we are confident in the results supporting the association between VO2peak and memory in the SD group. However, ultimately, these results will need to be confirmed with larger studies including a larger number of males, which were not sufficiently represented in this study.

CONCLUSION

The results of this study confirm the importance of sleep prior to encoding for the effective formation of episodic memory (14) and suggest that maintaining a high cardio-respiratory fitness level could have a protective effect against the effects of SD. Demonstrating that cardio-respiratory fitness protects memory against SD is the first step to justify the investigation of physical exercise as potential mitigation strategy against the effects of sleep insufficiency (6). These results, however, should be interpreted with caution. The fact that VO2peak explained only 41% of the variance in memory performance suggest that the protective effect of cardio-respiratory fitness against SD is possibly modest and that other factors may
play a mediating role. Well-designed randomized controlled trials will confirm if increasing cardio-respiratory fitness with exercise improves the capacity to encode, as well as consolidate, memories against the effects of different SD protocols (7). Finally, despite the results of the study are certainly promising, it is important to reiterate that exercise and achieving a higher cardio-respiratory fitness cannot be seen as long-term strategies to replace sleep (51). Besides its important role in memory formation and neuroplasticity (1), sleep is an essential biological function that is needed to maintain the homeostasis of multiple physiological systems.

ACKNOWLEDGEMENTS

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CONFLICT OF INTERESTS

The results of this study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. These results do not constitute endorsement by ACSM.
REFERENCES


34. Dal Maso F, Boudrias MH, Roig M. Acute Cardiovascular Exercise Promotes Functional Changes in Corticomotor Networks During the Early Stages of Motor Memory Consolidation. *Neuroimage*. 2017;0(0):0.


FIGURE CAPTIONS

Figure 1. Design of the study with the pre-screening and in-person visits undergone by the two experimental groups. Note that the sleep deprivation (SD) group did require only two in-person visits because they stayed in the laboratory to undergo the SD protocol and were already in the laboratory at the time of encoding. In contrast, the sleep control (SC) group required three visits because they had two come back to the laboratory for encoding. IPA-Q=International Physical Activity Questionnaire; PSQI=; Pittsburgh Sleep Quality-Index; ESS= Epworth Sleepiness Scale; PEBL= Psychology Experiment Building Language; GXT= Graded Exercise Test.

Figure 2. Bar plots showing hit rates (A), false alarms (B), and discrimination memory scores (d') (C) during the recognition task for both experimental groups. The sleep deprivation group (SD) showed worse hit rates ($t_{27}=-3.07; p=0.005; d=1.20$) and false alarm rates ($t_{27}=1.33; p=0.19; d=0.52$) than the sleep control group (SC), although only differences in hit rates were significantly different. The capacity to correctly discriminate (d’) between the original images and distractors was significantly poorer in the SD than in the SC group ($t_{27}=-3.68; p=0.001; d=1.44$). Bars represent means and error bars are standard error of the mean.

Figure 3. Scatter plots showing the associations between episodic memory performance (d’) and cardio-respiratory fitness (VO$_{2peak}$) adjusted for changes in fatigue for the SD and SC group. In the SD group (A), VO$_{2peak}$ and memory performance scores (d’) were significantly associated
In contrast, no association was found in the SC group ($R^2=0.23$; $F(2,7)=1.02$; $p=0.408$) (B). Regression lines are presented with corresponding 95% CIs.
Table 1. Characteristics of the participants of the study. Data are presented as means and standard deviations.

<table>
<thead>
<tr>
<th></th>
<th>SD (n=19)</th>
<th>SC (n=10)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>23.42(0.69)</td>
<td>23.00(2.66)</td>
<td>0.63</td>
</tr>
<tr>
<td>Male/Female</td>
<td>2/17</td>
<td>2/8</td>
<td>0.49</td>
</tr>
<tr>
<td>VO\textsubscript{2peak} (ml/kg/min)</td>
<td>39.27(10.51)</td>
<td>37.86(7.25)</td>
<td>0.67</td>
</tr>
<tr>
<td>Cognition (global score)</td>
<td>49.74(5.80)</td>
<td>50.48(3.30)</td>
<td>0.67</td>
</tr>
<tr>
<td>PSQI (global score)</td>
<td>3.68(1.29)</td>
<td>3.90(1.66)</td>
<td>0.72</td>
</tr>
<tr>
<td>ESS (global score)</td>
<td>4.95(3.39)</td>
<td>4.60(2.27)</td>
<td>0.74</td>
</tr>
<tr>
<td>IPA-Q (Total MET-minute)</td>
<td>2894.44(1837.71)</td>
<td>3119.90(1640.32)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

ESS= Epworth Sleepiness Scale; IPA-Q= International Physical Activity Questionnaire; PSQI= Pittsburgh Sleep Quality-Index.
**Table 2.** Responses omitted, response times, and arousal ratings at encoding and/or recognition. Data are presented as means and standard deviations.

<table>
<thead>
<tr>
<th></th>
<th>SD</th>
<th>SC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Encoding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responses omitted</td>
<td>2.89(3.14)</td>
<td>0.70(0.72)</td>
<td>0.07</td>
</tr>
<tr>
<td>Response time (ms)</td>
<td>1440.02(321.42)</td>
<td>1388.32(212.81)</td>
<td>0.65</td>
</tr>
<tr>
<td>Arousal rating</td>
<td>2.05(0.38)</td>
<td>2.04(0.34)</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Recognition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responses omitted</td>
<td>1.16(1.54)</td>
<td>0.90(1.66)</td>
<td>0.33</td>
</tr>
<tr>
<td>Response time (ms)</td>
<td>1257.27(175.39)</td>
<td>1257.19(142.87)</td>
<td>0.99</td>
</tr>
<tr>
<td>Response time hits (ms)</td>
<td>1204.23(146.28)</td>
<td>1151.28(127.24)</td>
<td>0.34</td>
</tr>
<tr>
<td>Response time misses (ms)</td>
<td>1232.75(165.18)</td>
<td>1311.05(198.29)</td>
<td>0.30</td>
</tr>
<tr>
<td>Response time correct rejections (ms)</td>
<td>1219.83(192.21)</td>
<td>1179.01(155.80)</td>
<td>0.57</td>
</tr>
<tr>
<td>Response time false alarms (ms)</td>
<td>1372.27(234.39)</td>
<td>1387.45(166.35)</td>
<td>0.87</td>
</tr>
</tbody>
</table>
The overall association between cardio-respiratory fitness (VO\textsubscript{2peak}) and memory (d’) in SC was not significant (R\textsuperscript{2}=0.23; p=0.408). In contrast, the association was found to be significant in SD (R\textsuperscript{2}=0.41; p=0.015).

<table>
<thead>
<tr>
<th>SC</th>
<th>β</th>
<th>SE</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.76</td>
<td>1.27</td>
<td>0.60</td>
<td>0.57</td>
</tr>
<tr>
<td>Cardio-respiratory fitness</td>
<td>0.02</td>
<td>0.03</td>
<td>0.79</td>
<td>0.45</td>
</tr>
<tr>
<td>Fatigue change</td>
<td>-0.02</td>
<td>0.01</td>
<td>-1.40</td>
<td>0.20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SD</th>
<th>β</th>
<th>SE</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.02</td>
<td>0.39</td>
<td>0.05</td>
<td>0.96</td>
</tr>
<tr>
<td>Cardiorespiratory fitness</td>
<td>0.03</td>
<td>0.01</td>
<td>2.84</td>
<td>0.01</td>
</tr>
<tr>
<td>Fatigue change</td>
<td>0.01</td>
<td>0.01</td>
<td>2.04</td>
<td>0.05</td>
</tr>
</tbody>
</table>
**Table 4.** Actigraphy data with sleep variables for each of the four nights after the memory encoding task. Data are presented for each night and their average using means and standard deviations. * Denotes a significant difference between groups (p<0.05).

<table>
<thead>
<tr>
<th></th>
<th>Night 1</th>
<th>Night 2</th>
<th>Night 3</th>
<th>Night 4</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SD</td>
<td>SC</td>
<td>SD</td>
<td>SC</td>
<td>SD</td>
</tr>
<tr>
<td><strong>TST (hours)</strong></td>
<td>9.53(2.24)</td>
<td>7.30(0.39)*</td>
<td>6.22(1.44)</td>
<td>6.36(0.52)</td>
<td>7.33(2.02)</td>
</tr>
<tr>
<td><strong>SOL (min)</strong></td>
<td>8.07(8.78)</td>
<td>3.00(7.35)</td>
<td>11.21(11.94)</td>
<td>15.00(17.60)</td>
<td>14.50(14.79)</td>
</tr>
<tr>
<td><strong>SE (%)</strong></td>
<td>88.53(2.47)</td>
<td>85.15(2.22)*</td>
<td>82.58(8.97)</td>
<td>79.88(5.52)</td>
<td>83.48(7.05)</td>
</tr>
<tr>
<td><strong>WASO (min)</strong></td>
<td>57.47(21.86)</td>
<td>65.87(12.95)</td>
<td>50.20(28.35)</td>
<td>70.25(24.49)</td>
<td>44.53(29.43)</td>
</tr>
</tbody>
</table>

SE=Sleep efficiency; SOL=Sleep onset latency; TST=Total sleep time; WASO=Wakefulness after sleep onset.
A

Discrimination index (d')

VO2peak

0 0.5 1 1.5 2 2.5

0 0.5 1 1.5 2 2.5

20 25 30 35 40 45 50 55 60 65
Discrimination index ($d'$) vs. VO2peak