Exercising the sleepless brain: exploring the potential protective effects on memory and neuroplasticity

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English Abstract

Introduction: Previous research in rodents has shown that cardiovascular exercise can protect memory from the deleterious effects of sleep deprivation (SD). However, human studies have yet to demonstrate the same protective effect. We investigated whether performing an acute bout of cardiovascular exercise after a night of SD could protect episodic memory encoding from the disruptive effects of sleep loss and explored potential neuroplasticity mechanisms that could mediate this effect using neuroimaging (electroencephalography – EEG), and the analysis of brain-derived neurotrophic factor (BDNF) in blood serum.

Methods: Twenty-eight healthy young participants underwent 30h of uninterrupted wakefulness after which they were allocated into either a sleep deprivation and exercise (SDE) group (n = 14) that performed 26 minutes (including a 3 min warm-up and a 3 min cool-down period) of cardiovascular exercise on a stationary bicycle at 80% of their maximal heart rate or a sleep deprivation only (SDO) group (n = 14) that rested on the bicycle, without pedaling, for the same duration. Following the intervention, participants viewed 150 images as the encoding part of the episodic memory task while wearing a 64-channel EEG cap to assess brain activity. Three days later, participants returned to the laboratory to perform the retention part of the episodic memory task, which required the visual discrimination of the 150 images previously presented from 75 new images introduced as distractors, while also wearing the EEG cap. Blood samples were collected at five timepoints: 9pm before SD, after 30h of SD and at 0-, 5- and 10- minutes post exercise or rest to assess the trajectory of BDNF levels. Group differences in memory performance were assessed with independent t tests and associations between BDNF levels after exercise or rest with episodic memory performance with Pearson's bivariate correlations. Although EEG methods are

described in this thesis, we decided to postpone EEG analysis, hence EEG results are not presented or discussed.

Results: The SDE group performed significantly better at identifying the original 150 images than the SDO group (mean difference [MD] [standard error {SE}], -0.12384 [0.04349]; p=0.0085) and showed a better overall score at the memory task (d'), although differences in this memory outcome were not statistically significant (MD [SE], -0.12571 [0.16696]; p=0.4583). The SDE group had more difficulty identifying the distractors but differences between groups was not significant (MD [SE], -0.04785 [0.03750]; p=0.2134). Comparison of BDNF levels pre- and post-SD showed that 30h of SD significantly increased BDNF levels (p=0.041). Furthermore, exercise significantly increased BDNF levels compared to baseline (p=<0.0001) and the difference immediately after exercise was significant compared to the rest intervention (p=0.002). The associations between BDNF levels and our memory outcomes showed that bigger areas under the curve were associated with better identification of the original images, although the correlation did not reach statistical significance (p=0.070)

Conclusions: These results provide preliminary support to the hypothesis that an acute bout of cardiovascular exercise performed after SD could have a protective effect on some aspects of episodic memory against the negative effects of sleep loss.

French Abstract

Introduction : Des recherches antérieures chez les rongeurs ont démontré que l'exercice cardiovasculaire pouvait protéger la mémoire des effets nocifs de la privation de sommeil (SD). Cependant, les études chez l'humain n'ont pas encore démontré le même effet protecteur. Nous avons investigué si le fait de réaliser une séance d'exercice cardiovasculaire après une nuit de SD pouvait protéger l'encodage de la mémoire épisodique contre les effets perturbateurs de la perte de sommeil, et avons exploré les mécanismes potentiels de neuroplasticité qui pourraient médier cet effet. Pour ce faire, nous avons utilisé la neuroimagerie (électroencéphalographie - EEG) et l'analyse du facteur neurotrophique dérivé du cerveau (BDNF).

Méthodes : Vingt-huit jeunes participants en bonne santé ont subi 30 heures d'éveil ininterrompu, après quoi ils ont été répartis soit dans un groupe privation de sommeil et exercice (SDE) (n = 14) qui a effectué 26 minutes (y compris une période d'échauffement de 3 minutes et une période de récupération de 3 minutes) d'exercice cardiovasculaire sur un vélo stationnaire à 80% de leur fréquence cardiaque maximale, soit dans un groupe privation de sommeil seulement (SDO) (n = 14) qui s'est reposé sur le vélo, sans pédaler, pour la même durée. Après l'intervention, les participants ont visionné 150 images lors de l'encodage de la tâche de mémoire épisodique tout en portant un casque d'EEG à 64 canaux pour évaluer l'activité cérébrale. Trois jours plus tard, les participants sont revenus au laboratoire pour effectuer le test de rétention de la tâche de mémoire épisodique, qui nécessitait la discrimination visuelle des 150 images précédemment présentées parmi 75 nouvelles images introduites comme distracteurs, tout en portant également le casque d'EEG. Des échantillons de sang ont été prélevés à cinq moments : à 21h avant la SD, après 30h de SD, et à 0, 5 et 10 minutes après l'exercice ou le repos pour évaluer la trajectoire des niveaux

de BDNF. Les différences de performance mnésique entre les groupes ont été évaluées par des tests t indépendants et les associations entre les niveaux de BDNF après l'exercice ou le repos et la performance mnésique épisodique par des corrélations bivariées de Pearson. Bien que les méthodes de collection des données d'EEG soient décrites dans ce mémoire, nous avons décidé de reporter l'analyse de ces données. Elles ne sont donc ni présentées ni discutées au cours de ce mémoire.

Résultats : Le groupe SDE a eu significativement plus de succès pour identifier les 150 images originales que le groupe SDO (différence moyenne [DM] [erreur type {ET}], -0,12384 [0,04349]; p=0,0085) et a obtenu un meilleur score global à la tâche de mémoire (d'), bien que les différences dans ce résultat mnésique ne soient pas statistiquement significatives (DM [ET], -0,12571 [0,16696]; p=0,4583). Le groupe SDE a rencontré plus de difficulté à identifier les distracteurs, mais les différences entre les groupes n'étaient pas significatives (DM [ET], -0,04785 [0,03750]; p=0,2134). La comparaison des niveaux de BDNF avant et après la SD a montré que 30 heures de SD ont augmenté de manière significative les niveaux de BDNF (p=0,041). De plus, l'exercice a augmenté de manière significative les niveaux de BDNF par rapport à avant celui-ci (p=<0,0001) et la différence immédiatement après l'exercice était significative par rapport au repos (p=0,002). Les associations entre les niveaux de BDNF et les résultats à la tâche de mémoire ont montré que de plus importantes aires sous la courbe étaient associées à de meilleurs taux d'identification des images originales, bien que la corrélation n'ait pas atteint une signification statistique (p=0,070).

Conclusions : Ces résultats amènent un soutien préliminaire à l'hypothèse qu'une séance d'exercice cardiovasculaire réalisée après la SD pourrait avoir un effet protecteur sur certains aspects de la mémoire épisodique contre les effets négatifs de la perte de sommeil.

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Contribution of Author

Béatrice Ayotte, student in the Integrated Program of Neuroscience of McGill University and member of the Memory Lab under the supervision of Dr. Marc Roig, is responsible for study design, ethics application, data collection and analysis of this study, and is the only author of this thesis.

List of Figures and Tables

List of Abbreviations (in alphabetical order)

AUC: Area under the curve

BDNF: Brain derived neurotrophic factor

EEG: Electroencephalography

ESS: Epworth Sleepiness Scale

HR: Heart rate

IPAQ: International Physical Activity Questionnaire

LTP: Long-term potentiation

MEQ: Morningness Eveningness Questionnaire

NREM: Non rapid eye movement sleep

PACES: Physical Activity Enjoyment Scale

PEBL: Psychology Experiment Building Language

PSQI: Pittsburgh Sleep Quality Index

REM: Rapid eye movement sleep

RPE: Rate of perceived exertion

SD: Sleep deprivation

SDE: Sleep deprivation and exercise

SDO: Sleep deprivation only

SWA: Slow wave activity

Introduction

Statement of problem

Sleep insufficiency has become a global problem which comes with tremendous cost at societal, economic, and public health levels [1]. Some of the most detrimental effects of sleep insufficiency on human health can be observed in the neurophysiological domain, including effects on neuroplasticity [2] and different aspects of cognition such as attention, sensory perception, and memory [3]. The increase of lifestyle factors affecting sleep such as lack of physical activity, unbalanced diet, electronic media use, and psychosocial stress among others [1] indicate that the global trend in sleep insufficiency will most likely not be improving anytime soon. In addition to preventive strategies, it is imperative for scientists to investigate potential mitigation strategies that could be used by individuals and clinicians alike to limit the negative effects resulting from lack of sleep.

Rationale

Sleep and exercise are two activities of seemingly opposite natures that may have synergistic effects on memory [4]. Sleep is essential for many memory processes including encoding, consolidation and reconsolidation [5], while various types of exercise [6], including both acute and long-term cardiovascular exercise, have also shown to improve different stages of memory [7]. Both acute and chronic sleep deprivation (SD), however, have adverse consequences on memory [4]. Animal studies show that cardiovascular exercise protects memory against SD by preserving neuroplasticity mechanisms involved in memory formation [4]. In contrast, very few human studies have investigated the protective effects of exercise on memory against SD [8] [9] [10] [11] and none of them explored the potential mediating role of neuroplasticity. This study will

be the first to investigate the potential neuroprotective effect of a single bout of exercise on episodic memory in situation of acute SD while focusing on the underlying neuroplasticity mechanisms that could mediate this effect.

Objectives and hypotheses

The main objective of this study was to determine whether a single bout of cardiovascular exercise performed after 30 hours of uninterrupted wakefulness, and immediately before the encoding of an episodic memory task, could protect episodic memory from SD and if neuroplasticity mechanisms mediate the protective effect. We assessed this using a combination of behavioral (episodic memory task) and neuroimaging (electroencephalography – EEG) techniques as well as a neuroplasticity biomarker (blood derived neurotrophic factor - BDNF) blood analysis. Although methods for collection of EEG data will be described in the following sections, results will not be presented, as analysis for this outcome has been postponed (see Brain activity section). We hypothesized that compared to the control resting condition, sleep-deprived individuals partaking in an acute bout of cardiovascular exercise post-SD would show:

1) better scores at the episodic memory task

2) greater levels of peripheral BDNF post-intervention and

3) more efficient brain activity patterns in cortical networks involved in directed attention during encoding and retention

4) significant associations between changes in BDNF levels and brain activity patterns with episodic memory

This would provide supporting evidence that, by preserving neuroplasticity, exercise could potentially protect memory encoding from the deleterious effects of SD.

Background

Types of memory

L. R. Squire (1987) was the first to suggest that memory could be categorized into two forms of memory, declarative and non-declarative, that have different operating characteristics and systems involved [12]. Declarative (explicit) memory is defined as the ability to acquire and retain information about facts (semantic memory) and events (episodic memory) [13], which can be consciously recollected, while non-declarative (implicit) memory involves abilities that can only be expressed through performance, such as non-associative learning, simple classical conditioning, priming, skills, and habits [14]. The term *procedural* memory used to be the chosen term to contrast with *declarative* memory, but it is now accepted that *procedural* relates to the skill-based kinds of learning and that certain memory types are not accurately represented by this term, hence the emergence of the more neutral term *non-declarative* [15]. Previous work in human amnesia has shown that only declarative memory, and not non-declarative, is impaired in this condition [12], suggesting that different brain systems are involved. Areas of the medial temporal lobe, which comprises the hippocampus, must be activated at the time of learning of declarative memories to form connections with the relevant cortical areas that represent the memory for a whole event, and form conjunctions with unrelated events [14]. The association of event and context, caused by the binding of cortical representations fostered by the hippocampus, allow the recollection of declarative memories [16]. Memories of the non-declarative domain, however, are not relying on this system, but rather on multiple brain systems depending on the non-declarative subtype, such as different perceptual areas of the cortex (and more specifically in the right posterior cerebral hemisphere), and the cerebellum, to name a few [15].

Stages of memory formation

A cascade of processes categorized in different stages must happen in order to transform experience-dependent information into a memory. The first stage, referred to as encoding, usually occurs during wakefulness when stimuli such as sounds, images, smells or sensorimotor information as well as the spatiotemporal context results in the formation of a new engram, which is initially unstable and susceptible to interference [17]. The second stage, consolidation, comprises the processes that take place during wakefulness and sleep [18] when the newly formed memory is stabilized by a strengthening and integration of the engram into preexisting knowledge networks [17]. The third stage is reconsolidation, which is defined as the reopening of a consolidation-like window that occurs when there is retrieval of the previously encoded and consolidated information [18]. Neuroimaging studies have shown that successful retrieval of information is associated with patterns of activation in the same cortical areas that were activated during encoding [19].

Sleep and memory interaction

Sleep helps maintain essential neuroplasticity mechanisms that will ensure proper memory encoding and consolidation, and thus learning capacity [20]. The interaction between sleep and memory can be better understood when integrated in the context of sleep architecture. A regular night of sleep is characterized by a weaving of cycles where stages of non-rapid eye movement sleep (NREM1, NREM2 and NREM3) are followed by rapid eye movement (REM) sleep [4]. Early sleep is characterized by predominant NREM sleep, whereas late sleep is characterized by predominant REM sleep and shorter stages of NREM sleep [4]. These different stages of the sleep-wake cycle can be distinguished by different frequencies and amplitudes of oscillatory brain

electrical activity. NREM1 sleep is characterized by predominant theta oscillations (4-8 Hz). NREM2 sleep, on the other hand, is typified by the apparition of sleep spindles (10-16 Hz), which can be described as rapid bursts of thalamocortical sigma waves, whereas NREM3 is mainly composed of slow delta waves (0.5-4 Hz), superposed with abundant sharp wave ripples of high frequency (100-300 Hz). REM sleep is mainly composed of theta and ponto-geniculo-occipital waves (6-10 Hz) [4]. These changes in neuronal dynamics during sleep can then be observed and interpreted to understand how mechanisms of neuroplasticity underlying memory processing occur in regard to the different stages of sleep [21].

Sleep is needed to restore the brain's capacity to encode new memories. The main hypothesis to explain the mechanisms behind this phenomenon is the synaptic homeostasis hypothesis, which states that sleep downscales the synaptic activity that has been increased during daytime memory encoding, thus allowing synapses to regain their homeostasis and be ready to start the encoding cycle again [4]. This downscaling of synapses primarily happens during NREM3 sleep, where slow wave activity (SWA) occurs [22]. This is supported by correlative evidence showing that the homeostatic regulation of SWA is associated with the synaptic potentiation (persistent strengthening of synapses) that happened during daytime, where the increase of potentiation is tied to a bigger increase in SWA during subsequent sleep [22]. If this downscaling of synaptic activity did not happen, synaptic plasticity would saturate, preventing the brain to acquire new information [22]. More recent studies have successfully shown a causal relationship between SWA and synaptic restoration by locally perturbing SWA (while maintaining general sleep architecture) in the sleep preceding the learning of a task [23] [24]. This perturbation was then translated as significantly decreased performance, as well as decreased hippocampal activation [24] and ability to exhibit synaptic potentiation [23], while unperturbed sleep increased

this ability. In contrast, a study that has enhanced SWA during a nap prior to the encoding of an episodic memory task has shown an increase in encoding ability compared to a sham control condition [25]. Sleep can then be considered as a necessary time investment for memory encoding [22]. The fact that sleep is necessary for memory encoding was also confirmed through behavioral experiments where participants went through an SD protocol prior to the encoding of a memory task, which translated as worse memory scores than sleep controls [26] [27].

A large body of evidence from both human and animal studies shows that sleep is also crucial for the formation of memories by fostering active consolidation [17] [20]. A striking example of this is shown through behavioral studies where improvements in both declarative [28] and non-declarative [29] memory tasks were observed after a night of sleep but not after a same amount of time of wakefulness during daytime. This would be explained in part by the hypothesis stating that sleep strengthens the synapses that have been activated during memory encoding by selectively reactivating them during slow wave sleep [30]. It is also during this reactivation process that the stabilization of memories occur due to the transfer of information from the hippocampus to the neocortex, with the two areas exhibiting increased connectivity and synchronous activity during sleep [30]. There is a correlational evidence for this phenomenon, where increases in SWA were observed following the encoding of declarative memory tasks [31], which have been linked with improvements in memory performance [31]. Similar improvements have also been observed with the increase of sleep spindles [32] [33], which are predominant in NREM2 sleep, in the sleep following declarative memory tasks. Perturbation of SWA in the sleep following the encoding of a task, on the other hand, has shown to impair memory performance [23], which confirms that sleep plays a role in the consolidation of memory. Previous evidence showed that REM sleep could potentially play a role in the consolidation of non-declarative memory [34], however, it is thought

that the impairments in memory observed in studies using a REM SD protocol might be a result of the stress resulting from these procedures rather than by the absence of REM sleep itself [35]. More recent studies have rather supported the role of NREM sleep in the consolidation of non-declarative memory, more specifically of sleep spindles that occur during NREM2 sleep [36] [37] [38].

Sleep deprivation and memory formation

SD does not only prevent the benefits of sleep, but rather has additional consequences due to extended wakefulness [39]. While sleep facilitates neuroplasticity and other memory-related mechanisms, SD has shown to impair the structural and functional mechanisms of memory formation [2] [23]. Animal studies have shown that SD modifies the structure and reduces the number of dendritic spines of the hippocampal CA1 neurons, which are considered as the physical correlates of memory [40], as well as neurons of cortical areas involved in memory tasks [41]. SD also severely reduces the excitability of hippocampal CA1 neurons and inhibits the long-term potentiation (LTP) of hippocampal synapses [42] [43]. All these negative effects prevent memories from properly forming by impacting both memory encoding and consolidation [41].

In addition, human studies using functional magnetic resonance imaging (fMRI) have shown that brain activity is decreased due to SD in key brain areas related to memory encoding such as the medial temporal lobe (specifically the hippocampus) as well as the dorsolateral prefrontal cortex, intraparietal sulcus, and the visual cortex, which are required for goal-directed attention during visual episodic memory encoding tasks [39]. In addition, learning-related hippocampal connectivity with perceptual regions (including the visual cortex) involved in memory tasks is also reduced as a result of SD [39]. In a study by Yoo et al. (2007), where

participants underwent 35 hours of SD prior to the encoding of an episodic memory task, impairments in brain activity were observed in the bilateral posterior hippocampal regions, which translated as worse subsequent retention. In studies where SD occurred after encoding, brain activity in the medial prefrontal cortex and the hippocampus during retrieval was significantly decreased in the sleep-deprived groups compared to the sleep controls [44].

Other studies have also shown that SD causes the downregulation of key signaling neuroplasticity molecules involved in memory processing such as BDNF [5]. Furthermore, it has been demonstrated that both acute and chronic SD have a dose-dependent effect on task performance, especially in terms of attentional impairments, indicating that increasing the duration of SD will worsen the effect on attention and performance in memory tasks [39].

Cardiovascular exercise and memory interaction

Acute and long-term cardiovascular exercise protocols of various durations and intensities have shown positive effects on both short-term and long-term memory [7]. However, since our work focuses on long-term memory, the present section will not discuss the effects of cardiovascular exercise on short-term memory. Acute interventions appear to have a greater overall positive effect on long-term memory than long-term interventions [7]. Acute exercise shows a moderate to large positive effect in both declarative and non-declarative tasks, while long-term interventions show a small but not significant effect on long-term memory [7]. In terms of modality, cycling has shown to be the most effective approach of acute intervention to improve long-term memory, but no particular mode of long-term intervention has been shown to be more beneficial [7]. The ideal duration of an acute bout of cardiovascular exercise to optimize long-term memory should be less than 40 minutes, regardless of the intensity [7]. However, duration of a

long-term cardiovascular program does not seem to have an impact on the magnitude of the improvement of long-term memory [7].

An important factor to consider when discussing the effects of cardiovascular exercise on memory is the timing of the intervention in relation to the exposure of the information that we wish to encode or consolidate [45]. The advantage with acute interventions is that they can have a specific effect on different stages of memory depending on when they are performed [45]. If an acute bout of exercise is performed before or during the encoding of the memory task, the effect it will have will be on encoding and possibly on early consolidation of the task [45]. However, if the acute bout of exercise is performed after encoding, only the consolidation will be targeted [45]. In long-term exercise interventions, we observe more of a cumulative effect on memory formation rather than a precise effect on one stage of memory formation or the other [45].

One of the mechanisms that could explain this effect is that cardiovascular exercise transiently increases the LTP of neural networks that are involved in a memory task and thus have an effect on encoding or consolidation depending on when the exercise bout is performed [45]. Cardiovascular exercise also increases the concentration of biomarkers such as lactate, norepinephrine and BDNF, which have been correlated with better long-term memory retention [46]. Furthermore, both cardiovascular exercise and higher levels of cardiovascular fitness, a surrogate of physical activity, have been associated with elevated levels of BDNF and larger hippocampal volume in both animal and human studies [7] [47]. BDNF is considered a primary candidate for neurogenesis stimulation (an indicator of neuroplasticity) in relation to exercise [47], which could explain this observed phenomenon. Considering the opposite nature of the effects of SD and cardiovascular exercise on neuroplasticity, it is not unrealistic to believe that

cardiovascular exercise could potentially counteract the deleterious effects of sleep loss on memory by promoting neuroplasticity [4].

BDNF and memory formation

BDNF is a secretory protein, part of the neurotrophic factors family, that is involved in assuring the survival and growth of neuronal populations in both the peripheral and central nervous system during development [48]. It is also implicated in regulating the structure and function of various neuronal circuits throughout life [48]. Numerous studies have concluded that BDNF plays a crucial role in different stages of memory including encoding and consolidation [49]. Some explanations of the positive effect of BDNF on memory are its role in synaptic plasticity by the facilitation of hippocampal LTP [50] and neurogenesis [47] . Considering that acute cardiovascular exercise increases BDNF levels [51], LTP activity can be prolongated to facilitate encoding and promote the stabilization of a memory engram into a long-term memory [45] as well as facilitating hippocampal memory processing [47]. A previous study in our lab has provided correlational evidence to the role of BDNF post-exercise and memory formation by showing that, in addition to increased BDNF levels after cardiovascular exercise, higher levels of BDNF are associated with better memory retention [46].

Animal studies on the protective effect of exercise on memory in SD

Many studies using rodents have investigated whether exercise could potentially protect memory against the negative effects of SD. However, all studies have done so in the context of long-term cardiovascular exercise programs and have not investigated the effect of a single bout of exercise (performed either before or after encoding) in a situation of SD.

Chronic cardiovascular exercise programs lasting between 10 days and 11 weeks have shown protective effects on a variety of memory tasks in acute SD episodes ranging from 12 to 96 hours, and most investigated what the potential mechanisms explaining this effect could be [4]. Some have found that the protective effect could be due to the prevention of the inhibition of LTP usually seen with SD [52] [53] [54] [55] and/or by preventing the downregulation of hippocampal BDNF cell activity [52] [53] [54, 55] [56] [57]. Some studies have rather looked at the potential preventive effect of exercise on oxidative stress and the improvement of antioxidant activity such as an experiment by Kholgi et al. (2023) that investigated the effects of treadmill programs using either mild or moderate intensities as well as 4-week or 10-week duration [58]. The results showed that both modalities improved memory when rats underwent a 24-hour SD protocol, but not a 4-hour SD protocol, which was not taxing enough [58]. They also showed that exercise indeed prevented the increase of oxidative stress and improved antioxidant activity, which could facilitate synaptic transmission and explain the preventive effect on memory [58]. Vollert et al. (2011) have also investigated this matter and shown that while SD increased oxidative stress in the cortex, hippocampus, and amygdala, 4 weeks of forced treadmill successfully prevented this increase [59].

Human studies on the protective effect of exercise on memory in SD

Despite the large documentation of the protective effects of cardiovascular exercise on memory in sleep deprived rodents, only four studies have attempted to replicate the same results in humans and none of them explored the potential mediating role of neuroplasticity mechanisms. JrLeDuc et al. (2000) were the first to investigate the effects of repeated bouts of moderate intensity cardiovascular exercise (for 10 minutes every two hours) during a 40-hour SD protocol on fatigue and alertness while also assessing cognition, including working memory, in a population of 12

aviators. The study showed that exercise transiently reduced short-term fatigue but had no effect on working memory [8].

Another study by Slutsky et al. (2017) investigated the effects of a single 15-minute bout of low intensity exercise on cognitive performance, including working memory, following 24 hours of SD in 22 healthy young adults. The results did not demonstrate any improvement in working memory performance due to exercise [9]. However, one important caveat of this study was that the SD protocol was not taxing enough (perhaps due to its relatively short duration compared to other SD protocols) to cause any memory impairments in the first place, so improvements could not be measured.

A chronic exercise study by Sauvet et al. (2020) investigated the effects of a 7-week 3 times a week cardiovascular training program of moderate to vigorous intensity on many aspects of executive function such as attention, inhibition and working memory after 40 hours of total SD on 16 young healthy men. While they found that cardiovascular training prevented the degradation of vigilance and attention that usually comes with SD, no positive effect on inhibition or working memory were observed [10].

A more recent study by Fleckenstein et al. (2022) has investigated the potential protective effect of a circuit training of moderate to vigorous intensity on cognition and false memories after a night of SD in 22 healthy young participants. The results have shown a protective effect of exercise on cognitive performance but could not prevent the occurrence of false memories [11]. One important limitation of this study is that since all participants underwent the SD protocol simultaneously and their wake-up time that day was not monitored, the duration of SD varied between participants. Furthermore, no method was implemented to measure the direct or indirect

physiological responses of participants to exercise (such as a heart rate monitor or a questionnaire on the rate of perceived exertion), so the intensity of the exercise bout varied among them.

It is important to note that most of these studies had working memory as their primary outcome. Working memory, defined as the temporary storage and manipulation of information [60], is not a memory function per se but rather an executive function [61]. In addition, most of these experiments had a relatively small sample size. The lack of consistency and consensus in terms of SD duration, exercise protocols and measured outcomes leaves a gap in the literature that needs to be filled. More studies are needed to determine if the protective effects of exercise on memory that has been observed in animals are applicable to humans and if so, investigate what could be the implicated neuroplasticity mechanisms that could mediate this effect.

Does cardiorespiratory fitness protect memory from SD?

Our first attempt at demystifying the complex relationship between exercise and memory in situation of SD was done through a behavioral study designed to investigate whether having a higher cardiorespiratory fitness (a surrogate of physical activity) could protect episodic memory encoding from the deleterious effects of SD [27].

Twenty-nine healthy young participants were allocated into either a sleep-deprived group (n = 19) or a sleep control group (n = 10). The sleep-deprived group underwent 30 hours of SD after which they had to view 150 images as the encoding part of the episodic memory task (more details on this episodic memory test are provided in a further section). The sleep control group performed the same encoding task, but after following a regular sleep routine rather than after SD. Four days later, participants came back to perform the retention part of the memory task where they had to identify the 150 original images from 75 new images introduced as distractors [27].

Cardiorespiratory fitness was determined through the maximal oxygen consumption (VO_2 peak) achieved during a graded exercise test performed at maximal intensity, which is considered as the gold standard measurement of cardiorespiratory fitness [62]. The primary outcome, which was defined as the ability to correctly discriminate the original images from the distractors, was significantly poorer in the sleep-deprived group than the sleep control group (MD [SE], -0.78 [0.21]; p=0.001). A regression analysis performed to determine the association between cardiorespiratory fitness and memory performance showed a significant correlation in the sleep-deprived group ($R^2 = 0.41$; p=0.015) but not in the sleep control group ($R^2 = 0.23$; p= 0.408) [27]. The difference in these results could indicate that it is only when memory encoding is challenged, in this case with a period of SD, that having a higher cardiorespiratory fitness could play a role in mitigating the negative effects.

This study concluded that SD indeed impairs episodic memory encoding, adding to the existing evidence that sleep is essential for this stage of memory, and provides preliminary evidence to the hypothesis that having a higher cardiorespiratory fitness could protect memory from the deleterious effects of SD.

Methods

Design

We designed a single blinded randomized controlled trial using a between-subject controlled design with a group allocation ratio of 1:1 that involved three visits (V1, V2 and V3).

Pre-visit: After the initial screening for inclusion and exclusion criteria, participants were asked to fill out questionnaires to identify sleep/mood disorders as well as their physical activity levels [63] [64] [65] [66] [67] to ensure eligibility to the study (see Pre-visit section). They were then randomly allocated into either a SD + Exercise (SDE) or SD only (SDO) group.

V1: Participants came to our laboratory to assess their cardiorespiratory fitness (VO_2peak) using a bicycle graded exercise protocol. Participants then performed three trials of the alertness test (see Fatigue, energy, and alertness section) [68] that was used during SD to familiarize themselves with the test and eliminate potential learning effects that could happen if they had been naïve to the test during SD. They were then provided with a sleep diary and wrist actigraphy to monitor their sleep/activity patterns until V3.

V2: Five days after V1, participants reported to the laboratory at 21:00. Upon arrival, a blood sample to measure baseline BDNF was drawn. Then they performed a battery of tests selected from the Psychology Experiment Building Language (PEBL; http://pebl.sourceforge.net) to assess their cognitive function (see Baseline cognition section). They then started a structured SD protocol [26], during which, every two hours, fatigue [69] and alertness [68] were assessed. After 29.5 hours of uninterrupted wakefulness, counting from the waking up time on the day of V2, a 64-channel EEG cap was mounted on each participant's head. After 30 hours of uninterrupted wakefulness participants performed the alertness test and filled the fatigue questionnaire, and a second blood sample to assess BDNF levels after SD was drawn. Participants

then performed either 20 minutes of exercise (SDE) or rest (SDO). Following that, three more blood samples were drawn to assess BDNF levels immediately, as well as 5- and 10- minutes after the exercise or rest interventions [46]. Participants then again performed the alertness test and filled out the fatigue and physical activity enjoyment questionnaires, and started the encoding part of the episodic memory task while brain activity was recorded with EEG [8].

V3: Three days after V2, participants reported to the laboratory to perform the retention part of the memory task [26], during which brain activity was again monitored with EEG. Participants were instructed to avoid vigorous physical activity 24 hours prior to each in-person visit.

Figure 1: Overview of the study design

Participants

Inclusion & exclusion criteria

Thirty healthy participants (males and females) aged between 18 to 35 were recruited (see Sample Size Estimation section for more details.). They were included if they had a regular sleeping schedule (6h+ sleep, bedtimes between 9pm-1am and wake-up times between 6am-10am) for at least 5 days prior to V2 as assessed by actigraphy and sleep diary. They were excluded if they: **a)** had a history of diseases affecting memory or sleep; **b)** were taking sleep aids or medications/drugs affecting the nervous system; **c)** had contraindications to exercise; **d)** worked night shifts; **e)** had been on a trans-meridian trip in the month prior to the study; or **f)** consumed three or more servings of stimulants (e.g., coffee, tea, energy drinks) per day. They were also excluded if: **g)** their score at the Pittsburgh Sleep Quality Index (PSQI) was greater than 5 [63] and/or if **h)** their score at the Epworth Sleepiness Scale (ESS) was equal to 10 or more [64].

Recruitment

Participants were recruited from social media announcements as well as email lists from McGill University. The study was also advertised through posters that were displayed both physically and digitally in locations of interest (universities, yoga studios, Facebook groups of paid research studies, etc.)

Allocation

Participants were randomly allocated into either a SD + Exercise (SDE) or SD only (SDO) group. They were allocated using a sequence created and held by a central randomization service (randomizer.org).

Assessments

Pre-visit

Participants were first be screened via email using the exclusion/inclusion criteria, as well as the Pittsburgh Sleep Quality Index (PSQI) [63] and Epworth Sleepiness Scale (ESS) [64] to determine eligibility. The International Physical Activity Questionnaire (IPA-Q) [65], an adapted version of the Physical Activity Enjoyment Scale (PACES) [66], and the Morningness-Eveningness Questionnaire (MEQ) [67] were also used to assess and compare physical activity habits and diurnal preference of the participants.

The PSQI is a self-reported questionnaire assessing sleep quality of the last month through seven components (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction) [63]. Each component gives a score that is converted to a global score, for which the cut-out score of 5, distinguishing good from bad sleepers, was used as one of our exclusion criteria.

The ESS is a short questionnaire assessing daytime sleepiness where participants will rate their chance of dozing off in eight different circumstances (e.g., being a car passenger for more than an hour) to give a final total score. Total ESS scores successfully distinguish normal from pathological sleepiness from various conditions such as narcolepsy or idiopathic hypersomnia [64] with a cut-out score of 10. We used this cut-out as one of our exclusion criteria to disqualify participants with potential sleep problems.

The IPA-Q is an internationally validated questionnaire that assess sedentary, moderate, and vigorous physical activity levels in different life areas such as work, leisure time, transportation, gardening/yard work and household chores [65]. We used this questionnaire to

determine which protocol is best suited for the participant's fitness level in the maximal graded exercise test.

The PACES is a questionnaire meant to assess general enjoyment towards exercise that we used to assess the participants' general feelings toward cardiovascular exercise. We created an adapted version of the PACES, containing 8 items that participants were asked to rate on a 7-point scale (e.g. 1 = cardiovascular exercise is no fun at all, 7 = cardiovascular exercise is a lot of fun) [66] that we have used previously [70]. Higher scores (of a minimum score of 8 and a maximum score of 56) indicate greater enjoyment. We used this questionnaire to ensure that there are no significant differences between the two experimental groups and/or outliers in terms of participants' perception of physical activity.

The MEQ is a questionnaire containing 19 questions selected to assess morningness-eveningness of participants based on their circadian rhythm and classify them between evening, intermediate or morning type [67]. The scores of each question is added to give a final score between 16 and 86, which can then be used to classify participants as either definite evening type (score between 16 and 30), moderate evening type (31 to 41), intermediate type (42 to 58), moderate morning type (59 to 69) and definite morning type (70 to 86) [67]. We used this questionnaire to ensure that there are no significant differences between the two experimental groups and/or outliers in terms of participants' diurnal preferences.

These questionnaires have been used extensively and have been validated in previous studies [71] [72] [73] [66] [67]. If deemed eligible, participants were then invited to come to our laboratory for V1, where cardiorespiratory fitness (VO_2peak) was assessed through a graded exercise test.

Graded exercise test

At V1, participants underwent a graded exercise test on a stationary bicycle to assess cardiorespiratory fitness (i.e., oxygen consumption -VO_2peak-). During this test, heart rate (HR), oxygen consumption and the rate of perceived exertion (RPE) were monitored continuously. The RPE, assessed with the Borg scale, is valid and reliable to assess workloads in healthy individuals [74]. The test started with a 3-minute warm-up where participants pedaled against a resistance of 50 or 75 Watts (W), depending on their fitness level as assessed with the IPA-Q [65]. After the warm-up, the intensity was increased by 10 to 20 W per minute [65] until participants could not cycle anymore. During the test, participants were required to maintain a cadence of at least 70 rpm. The test then ended with a 3-minute cool-down period, where participants cycled with no resistance.

Actigraphy

Actigraphy is a reliable and well validated tool for the measurement of overall activity and sleep/wake cycles for people in everyday life [75]. Participants were given an actigraphy watch to wear from V1 to V3. Data regarding participants' physical activity, sleep/wake cycles, and sleep efficiency was then provided. Actigraphy data in this study was crucial to ensure the 30 hours of SD were met and to assess sleep and activity cycles prior, during and after SD.

Sleep Diary

At the end of V1, participants were given a sleep diary to fill out until V3 [76]. Along with the actigraphy data, the sleep diary data recorded for the 5 days prior to V2 confirmed if they had followed a regular sleep schedule (bedtime between 9pm and 1am and wake-up time between 6am

and 10am, with 6+ hours of sleep each night) before partaking in SD. The sleep diary was also used to cross-validate the data from the actigraphy watch.

Fatigue, energy, and alertness

Fatigue was measured using the Visual Analogue Scale to Evaluate Fatigue Severity (VAS-F), a tool that has shown good validity and reliability to assess differences in fatigue and energy levels [69]. The scale contains 13 items to assess fatigue and 5 items to evaluate energy, where participants are asked to rate each item from 0 to 10. Fatigue was assessed every two hours throughout the SD protocol. Alertness was measured with the Sleep-2-Peak® application on an electronic tablet (SM-T280, Samsung) which has been validated for assessing changes in alertness during periods of SD [68]. This application required participants to tap the screen of the device with their index finger every time a sun appeared on the screen at random intervals. Their average reaction time was calculated over 10 trials and used as a surrogate of alertness. This test was performed three times at V1 for participants to familiarize with the task and every two hours during the SD protocol to assess changes related to SD. It was also performed before retention. It has been demonstrated that both acute and chronic SD have a dose-dependent effect on attention and thus alertness (sustained attention) levels were expected to decrease as SD time increased [39].

Baseline cognition

Baseline cognition was assessed with a battery of tests selected from the PEBL, a cross-platform open-source system containing approximately 70 cognitive tests that can be implemented in behavioral and neuroscience experiments [77]. For the purpose of our study, we designed a battery of tests to measure different cognitive functions such as inhibition, episodic memory,

working memory, executive function, and processing speed using five tasks: the Flanker test; where participants responded to the center stimulus in a background of misleading flankers [78], the Buildup; a memory span task involving a spatial response [77]; the Corsi test; which focuses on short-term memory of visual sequences [79], the Stroop colour test; in which participants made a one-dimensional response in a situation with multi-dimensional stimuli [80] and the pattern comparison test, which required to compare two pattern grids as quickly and accurately as possible [81]. We have selected these tasks because they are not language-dependent, and they test the same cognitive functions used in previous studies [82]. The battery required approximately 30 minutes to be completed.

Interventions

SD Protocol

Participants were asked to avoid the consumption of caffeinated beverages 12 hours prior to the night of SD. The SD protocol consisted of standardized light activities such as board games or drawing and included 5 minutes of walking every hour to limit discomfort resulting from uninterrupted wakefulness while controlling for potential confounders (e.g., changes in arousal level, physical activity) [26]. Screen time was limited to 2 hours for the whole protocol, with no more than 30 minutes at a time and was not permitted for the last hour prior to the exercise or rest intervention [83]. This limit was imposed to minimize reduction of melatonin and increases in alertness caused by blue-light exposure [84] [85] [86]. Participants were monitored by the researchers during the whole SD protocol.

Exercise intervention

The cardiovascular exercise bout was performed on a stationary bicycle. This exercise protocol has shown to provide stimulus to improve memory without causing long-term fatigue [87] [88]. Participants in the SDE group performed this acute bout of aerobic exercise following the 30 hours of SD. Results from the graded exercise test performed at V1 was used to determine the workload of each participant for this bout of exercise. The protocol started with 3 minutes of warm-up at 60% HRmax and was followed by 20 minutes of exercise at the predicted resistance to attain 80% HRmax. During these 20 minutes, participants were required to maintain a cadence of 70 rpm. Following this bout, participants cycled at 0 W for an additional 3 minutes for a cool-down period, for a total of 26 minutes spent on the bicycle. In addition to HR, RPE was assessed to evaluate participants' workload during the acute exercise bout. Percent HRmax was maintained within ±5 beats per minute by adjusting workload during exercise. The training intensity was monitored with a HR Polar® monitor combined with the RPE assessed with the 6-20 Borg scale [89]. The HR monitor was wirelessly connected to an iPad® through Polar Team®, an application that provides real-time visual feedback on individually set HR-based training targets. RPE was assessed at the beginning of the session (i.e., before warm-up), after warm-up and every two minutes during the 20 minutes of the main component of the session (i.e., before cool-down), and after cool-down. HR, RPE and workload data (e.g., time, distance) were entered manually in training logs.

Control (rest) intervention

Participants in the SDO group underwent the same protocol as the exercise group, but instead of exercise, they were sitting on the bicycle, without pedaling, for the same duration (total

of 26 minutes: 20 minutes + 3 minutes equivalent to the warm-up period and 3 minutes equivalent to the cool-down period). HR was also monitored with a Polar® monitor and the RPE was assessed with the 6-20 Borg scale [89]. These measures were taken at the same timepoints used for the exercise intervention to allow comparisons.

Outcomes

The primary outcome of the study is episodic memory. Our secondary outcomes are brain activity and BDNF levels. Details of the outcomes and how they were measured are provided below.

Episodic Memory

The episodic memory task that we used was composed of an encoding session and a retention session. This task has been shown to be sensitive to the effects of SD and has previously been used and validated by Yoo et al (2007) as well as our laboratory in our recent study investigating the effect of VO_2peak on memory in SD [27]. Both tasks were performed while participants were wearing the EEG cap to measure brain activity.

Encoding: After 30 hours of uninterrupted wakefulness and after the exercise or rest intervention, the participants were shown 150 neutral images (including people, landscapes, objects) divided into 5 runs of 30 pictures. A fixation crosshair appeared for 2000ms, after which participants had 3000ms to visualize the image and determine their level of arousal (rated between 1 and 4, 1 being the minimal and 4 the maximal level of arousal) as response to the picture by pressing a keypad button (RB-740, Cedrus). The arousal rating task was used to ensure participants were paying attention to the image and were not falling asleep. Since the internal state (such as emotions or perceptions) of the individual performing the task have a blueprint on episodic

memory [90], we chose neutral images to minimize any potential emotional component. A common problem associated with picture recognition tests used to assess episodic memory is that the participant is often instructed to memorize the learning material, which is likely to activate semantic memory systems rather than episodic systems [90]. To account for this, no instructions about the upcoming retention test was provided at encoding. Rather, participants thought the test had to do with arousal assessment rather than memory, preventing any form of rehearsal that could be performed between encoding and retention.

Retention: The participants were shown the same 150 images, intermixed with 75 new images introduced as distractors. The participant was then asked if they had seen the image during encoding or if the image was a distractor. They had 3000ms to view the image and answer whether they had seen the image on the preceding visit or not.

A memory score was attributed following the completion of the encoding and retention tasks, where images viewed during the encoding task were referred as "originals" and the added images viewed during the retention task were referred as "distractors". The score that resulted from the retention of the memory task was composed of the following different outcomes: original images correctly identified (hits), original images incorrectly identified (misses), distractors correctly identified (correct rejections) and distractors incorrectly identified (false alarms). We then converted those outcomes in two memory rates, the hit (hits/original images) rate and the false alarm (false alarms/distractors) rate [26]. Our primary outcome of memory performance was the capacity to discriminate between old and new images, which we calculated with a discrimination index (d') obtained by subtracting the z score of the false alarm rate from the z score of the hit rate [91].

Brain activity

*Note that we decided to expand this study by adding two other intervention groups, and all EEG analyses will be performed when data collection for these new groups will be complete. Thus, the EEG results have not been analyzed and will not be discussed in this thesis.

We mounted a 64-channel EEG cap on participants' heads prior to both encoding and retention of the memory task. Along with our EEG system, we used a StimTracker®, a device that detects the onset of stimulus to set a marker in the EEG data collection to facilitate analysis. We placed the sensor of the StimTracker® on the screen where the images appeared during the encoding and retention tasks. Every time a new image appeared on the screen and every time the participant pressed on a keypad button the EEG file was marked with a time stamp. This allowed us to assess brain activity while participants were viewing the image and deciding on their response (determine arousal level during encoding or assessing recognition during retention).

The activity of cortical networks involved in directed attention during encoding and retention [26] will be assessed by measuring event-related desynchronization in electrodes located on regions of interest. EEG signals will be computed in the alpha, beta, and theta bands [92]. Since no previous study has investigated brain activity in SD during the encoding of memory task following a bout of exercise or rest, the results of this analysis remain to be seen. A previous study [8] that looked at brain activity during SD following repeated exercise or rest bouts during a seated period has shown that exercise induced an increase in theta activity compared to rest at electrodes C3, C4 and Pz. However, no significant differences could be observed between exercise and rest in alpha activity. Differences in beta activity between the two conditions varied depending on the time of the day, with activity at C3 and Pz being at times higher in the exercise condition than the rest condition and at times lower, but beta activity at C4 was lower in exercise than in rest.

BDNF levels

Participants were required to reach our facilities for V1 in a fasting state (no eating 3 hours prior to the visit). A nurse then withdrew a 5-ml blood sample from the brachial artery of the non-dominant hand of the participant. The sample was placed into lab tubes and was then kept at room for 60 minutes, refrigerated for 30 minutes and finally centrifuged at 5000 rpm. Blood serum was pipetted into lab wells and stored in a -80℃ freezer. The assessment required 5 minutes to be completed. This was repeated after 30 hours of SD and three more times after the exercise (SDE) or rest (SDO) intervention (at 0-, 5- and 10-minutes post-intervention). The total of five samplings per participant allowed us to determine the trajectory of peripheral serum BDNF levels pre- and post-SD as well as after exercise or rest. BDNF levels were assessed with enzyme-linked immunosorbent assay (ELISA) kits (Biosensis).

Ethical considerations

Our main ethical consideration for this project was the mode of transportation by which participants returned home following the period of SD. To ensure participants returned home in the safest way possible after SD, we asked them to confirm at V1 their chosen way of going back home between transit, taxi services or rideshare. A refund for any travel-related cost after SD was provided upon presentation of proof of payment.

Data analysis

Sample Size Estimation

Our aim was to have a sample size large enough to detect differences between groups in the capacity to correctly identify (d') the 150 images presented at encoding using independent t-

tests. It was difficult to base our estimation on previous data since no study has investigated the protective effect of acute exercise on episodic memory encoding during SD in humans. We based our sample size on a previous study that used the same episodic memory paradigm and a similar SD protocol [26]. The effect size value of that study [26], calculated from the subtraction of mean differences between the two groups divided by the pooled standard deviation, was 3.01. Using a more conservative effect size of 1.5 with an allocation ratio of 1:1, we estimated that we needed a minimum of 13 participants in the SDE group and 13 participants in the SDO group to be able to detect significant differences (α=0.05) in episodic memory performance (d') with a power (1- β err prob) of 0.95. We decided to round the sample size to 30 participants total (15 per group) to account for dropouts or missing data.

Statistical Analysis

Analyses were carried out with JMP Pro® version 17. We first plotted data using histograms and normal quantile plots to visualize all 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 and Wilcoxon rank sum tests and Chi-square tests for continuous and categorical variables respectively. Independent t-tests were used to determine differences between groups for measures of fatigue, energy, alertness, sleep, and episodic memory. We also performed a mixed model ANOVA with a between-subject factor of group and a within-subject factor of time for data with multiple time points such as fatigue, energy levels, alertness, and BDNF levels. Using multivariate analysis, we explored the impact in which variables such as age, sex, VO_{2peak}, cognitive status, fatigue or alertness could influence differences between groups. To compare BDNF levels pre- and post-

SD, we performed a matched paired t-test between these two time points including both groups. BDNF levels at 0- 5- and 10 minutes post-intervention for both groups were normalized to the baseline post-SD levels by dividing BDNF levels post-intervention by the level post-SD. To assess differences between groups in the BDNF response to the intervention we fitted a mixed model with BDNF as dependent variable, group and time point as fixed factors, and subject as random factor. The auto-regressive of order -1 (AR-1) covariance structure was used as correlation structure. We used Pearson's bivariate correlations to explore associations between the area under the curve (AUC) of BDNF after exercise or rest (our secondary outcome) with episodic memory performance (d', our primary outcome, as well as hit rate and false alarm rate). AUC was calculated using MATLAB R2023a using the trapezoidal function (trapz). We chose to report AUC rather than BDNF peaks to capture and compare the changes in BDNF levels' trajectory at different timepoints. All analyses were performed with 2-tailed probability tests with the statistical level (α) set at 0.05. The results of between groups comparisons are reported as mean differences (MD) and standard errors (SE).

Planned subgroup analysis: sex and gender

Biological sex affects the physiological responses to exercise [93] and it is already well-known that there are substantial differences in the responses between males and females in regards to sleep [94] and sleep deprivation [95]. One of the main differences between individuals of opposite biological sex is the presence of menses and how different phases of the menstrual cycle affects sleep [96]. Females in their follicular phase (phase before ovulation) have longer deep sleep duration and report better sleep quality compared to those in their luteal phase (phase after ovulation before menses) [96]. Luteal phase is also characterized with less REM sleep and more

frequent insomnia [96]. However, we did not take menstrual cycle phase into account when collecting data, which could be considered as a limitation (see Potential Problems and Limitations section).

We are not aware of any study demonstrating a direct influence of gender on the responses to exercise, sleep, or sleep deprivation. However, gender may affect the preferences and motivation for different physical activities [97], which could affect compliance or feeling towards the exercise intervention.

The influence of biological sex on the effect of exercise on primary and secondary outcomes was explored by conducting subgroup analyses. Sex has been categorized as a binary variable (female/male) based on self-declared sex at birth for each participant. With our small sample size, it has been deemed unrealistic to think that we could find a correlation between gender and any of our outcomes, therefore, gender as a variable was not explored in our analysis.

Results

Demographics

A total of 31 participants were recruited, but one participant withdrew themselves from the study before V2, meaning that 30 participants (15 in each group) completed all three visits. One participant in the SDE group had a negative value of d', which was lower than the mean by more than two standard deviations, and which was something previously unseen in all studies we conducted using this protocol. This participant was therefore considered as an outlier and removed from the study. Another participant in the SDO group was also considered as an outlier due to the omission of 26 responses at retention because they were dozing off during the task due to poor sleep the night before. Considering that the omissions lower the total memory score and that the participant's omissions were due to another reason than poor memory retention, the data from this participant was also excluded. The removal of these two participants' data did not change the results of the study. The data of 28 participants (14 per group) was therefore analyzed. The two groups did not show any significant differences in terms of biological sex, age, cardiorespiratory fitness (VO_2peak), cognitive status or in any of the questionnaires' related data such as sleep quality, physical activity level and enjoyment, or diurnal preference, as assessed by the PSQI, ESS, IPAQ, MEQ and PACES (see Table 1. below for all details).

Table 1: Demographics of participants. Data are presented as means and standard deviations.

	SDE (n=14)	SDO (n=14)	p-value
Age (y)	25.57 (3.55)	23.71 (4.94)	0.264
Sex (Male/Female)	6/8	9/5	0.256
VO_2 Peak (ml/kg/min)	41.26 (8.24)	40.82 (7.02)	0.882
PSQI (global score)	4 (1.04)	3.86 (1.35)	0.756
ESS (global score)	5.86 (2.57)	5.71 (2.64)	0.886
IPAQ (total MET-min)	5009.07 (2736.65)	4728.57 (2417.32)	0.776
PACES (global score)	46.71 (7.36)	45.5 (5.23)	0.620
MEQ (global score)	50.82 (12.79)	50.33 (9.98)	0.925
Cognition PEBL (global score)	50.04 (0.54)	50.01 (0.6)	0.894

Sleep & actigraphy pre-, during and post-SD

The sleep diary and actigraphy data prior to SD showed that all participants followed a regular sleep schedule 5 days prior to V2 and that the total sleep time was similar between groups (MD [SE], 4.929 [18.454]; p=0.792). The average sleep efficiency, defined as the ratio between the time spent asleep and the time spent in bed dedicated to sleep, was also similar between both groups (MD [SE], -1.045 [1.790]; p=0.565). The average number of sleep interruptions per night recorded in the 5 nights prior to SD was not different between groups (p=0.840) with the SDE group reporting an average of 3.29(1.85) interruptions and the SDO an average of 3.5(3.29) interruptions. Similarly, the average daily average activity counts in the 5 days prior to SD were similar between groups (MD [SE], 19.647 [32.816]; p=0.555), suggesting no differences in physical activity patterns pre-SD. The average activity counts during SD were also very similar,

with no significant differences between groups (MD [SE], -11.666 [27.671]; p=0.677) (see Table 2 for more information on the sleep and actigraphy data).

Similar results were observed for the sleep and activity data post-SD. Both groups slept a similar amount the night after SD (MD [SE], -21.640 [40.950]; p=0.603) and had a similar sleep efficiency (MD [SE], -2.626 [1.908]; p=0.185). The same can be said for the 3 nights that followed SD, prior to the retention task, with similar sleep time (MD [SE], -13.000 [23.010]; p=0.578) and efficiency (MD [SE], -3.021 [1.702]; p=0.090) between groups. The average number of sleep interruptions per night recorded in those 3 nights was also similar between groups (p=0.545) with the SDE group reporting an average of 3.33(1.8) interruptions and the SDO an average of 3.93(3.11) interruptions. Similarly, the average daily average activity counts in the 3 days after SD and prior to the retention task was similar between groups (MD [SE], 17.450 [37.083]; p=0.642), suggesting no differences in physical activity patterns post-SD.

Table 2: Sleep and actigraphy data pre-, during and post-SD. Data are presented as means and standard deviations

	SDE	SDO	p-value
Avg. sleep pre-SD	7h25 mins (40.93)	7h30 mins (55.61)	0.792
Avg. sleep efficiency pre-SD	92.04 (3.81)	90.99 (5.51)	0.565
Avg. activity count pre-SD	369.83 (89.37)	389.48 (80.47)	0.555
Avg. activity count during SD	318.72 (87.1)	307.06 (55.97)	0.677
Avg. sleep 1st night post-SD	12h39 mins (77.54)	12h12 mins (132.16)	0.603
Avg. sleep efficiency night post-SD	96.43 (3.04)	93.81 (6.46)	0.185
Avg. sleep post-SD	9h25 mins (46.79)	9h12 mins (72.27)	0.578
Avg. sleep efficiency post-SD	94.54 (3.19)	91.52 (5.51)	0.090
Avg. activity count post-SD	364.19 (98.36)	381.64 (97.87)	0.642

Fatigue, energy, and alertness

The level of fatigue of participants (assessed by the VAS-F) at pre-SD (10pm) was not significantly different between groups (MD [SE], -5.714 [6.767]; p=0.407) and neither at 30h SD (MD [SE], 8.071 [11.959]; p=0.506) or after the exercise or rest condition (post-int) (MD [SE], 11.462 [14.846]; p=0.449). The level of energy (also assessed by the VAS-F) was not significantly different between groups at pre-SD (MD [SE], -1.143 [3.096]; p=0.715) or at 30 hours of SD (MD [SE], -5.357 [3.895]; p=183) but was indeed significantly different post-int (MD [SE], -11.652 [4.426]; p=0.018), with the SDE group reporting having significantly more energy (22.83 [13.51]) than the SDO (11.18 [6.94]) group (p=0.018). Differences in fatigue levels between pre-SD and 30 hours of SD or between 30 hours of SD and post-int were not statistically different between groups (MD [SE], 13.071 [12.023]; p=0.287) and (MD [SE], 5.606 [6.736]; p=0.415), nor was the difference of energy levels between pre-SD and 30 hours of SD (MD [SE], -3.500 [4.245]; p=0.418). In contrast, the difference of energy levels between 30 hours of SD and post-int was significantly different (MD [SE], -6.780 [3.139]; p=0.047), with the SDE group having a greater positive difference in energy level post-int (7.42 [9.9]) than the SDO group (0.64 [4.3]). The results of our two-way (group X timepoint) ANOVA repeated measures analysis did not show any significant group x time interactions for fatigue levels ($F(2,49)=1.45$;$p=0.24$). However, we did find significant group x time interactions for energy levels ($F(2,49)=3.22$;$p=0.0487$). Only energy levels immediately after the exercise or rest intervention reached statistical significance (MD [SE], 12.159 [3.992];p=0.0409), with the SDE group reporting higher energy levels.

The baseline levels of alertness assessed as reaction times by the Sleep-2-Peak® were not significantly different between groups at pre-SD (MD [SE], 23.500 [15.857]; p=0.152), nor at 30 hours of SD (MD [SE], 12.786 [13.474]; p=0.352), or post-int (MD [SE], 4.795 [14.712];

p=0.748). Differences in alertness levels between pre-SD and 30 hours of SD or between 30 hours of SD and post-int were also not statistically different between groups (MD [SE], -11.786 [12.442]; p=0.356) and (MD [SE], 7.833 [11.593]; p=0.507). Similar results were found for the alertness levels at V3 pre-retention (MD [SE], 0.643 [11.813]; p=0.957). The results of our two-way (group X timepoint) ANOVA repeated measures analysis did not show any significant group x time interactions for alertness levels (F(2,47)=0.364;p=0.697).

Physiological responses during interventions

Participants in the SDE group had an average HR of 146 bpm during the exercise intervention which corresponded to an average of 79.3% of their HR max. Participants in the SDO group, on the other hand, had an average HR of 68 bpm during the rest intervention, which corresponded to an average of 36% of their HR max. Both of these values were significantly different (p=<0.0001). Similarly, their RPE were also significantly different (p=<0.0001), with an average RPE of 14.04 on the 6-20 Borg scale [89] during exercise for the SDE group, compared to 6.15 during rest for the SDO group.

Behavioral responses of the memory tasks

At encoding, there were no significant differences between groups in the number of responses omitted (MD [SE], -0.286 [1.950]; p=0.885) or in the arousal rating (MD [SE], -0.114 [0.119]; p=0.350)., However, the response time to rate arousal when viewing the image was significantly different (MD [SE], -223.270 [95.820]; p=0.028), with the SDE group taking longer to respond (1547.34 [209.44]) compared to the SDO group (1324.07 [274.78]). This does not mean

that the SDE group viewed the images for longer, as the images remained on the screen for the whole 3000ms despite when arousal rating was done. At retention, no significant differences were observed between groups in the number of responses omitted (MD [SE], 0.500 [0.872]; p=0.573), or overall response time during the task (MD [SE], -64.940 [70.300]; p=0.364). Similarly, no significant differences were observed between groups in response times for trials marked as hits (MD [SE], 1.860 [62.210]; p=0.976), misses (MD [SE], -101.070 [82.890]; p=0.234), correct rejections (MD [SE], -57.740 [77.040]; p=0.460), or false alarms (MD [SE], -102.810 [98.210]; p=0.305) (see Table 3. below for all details).

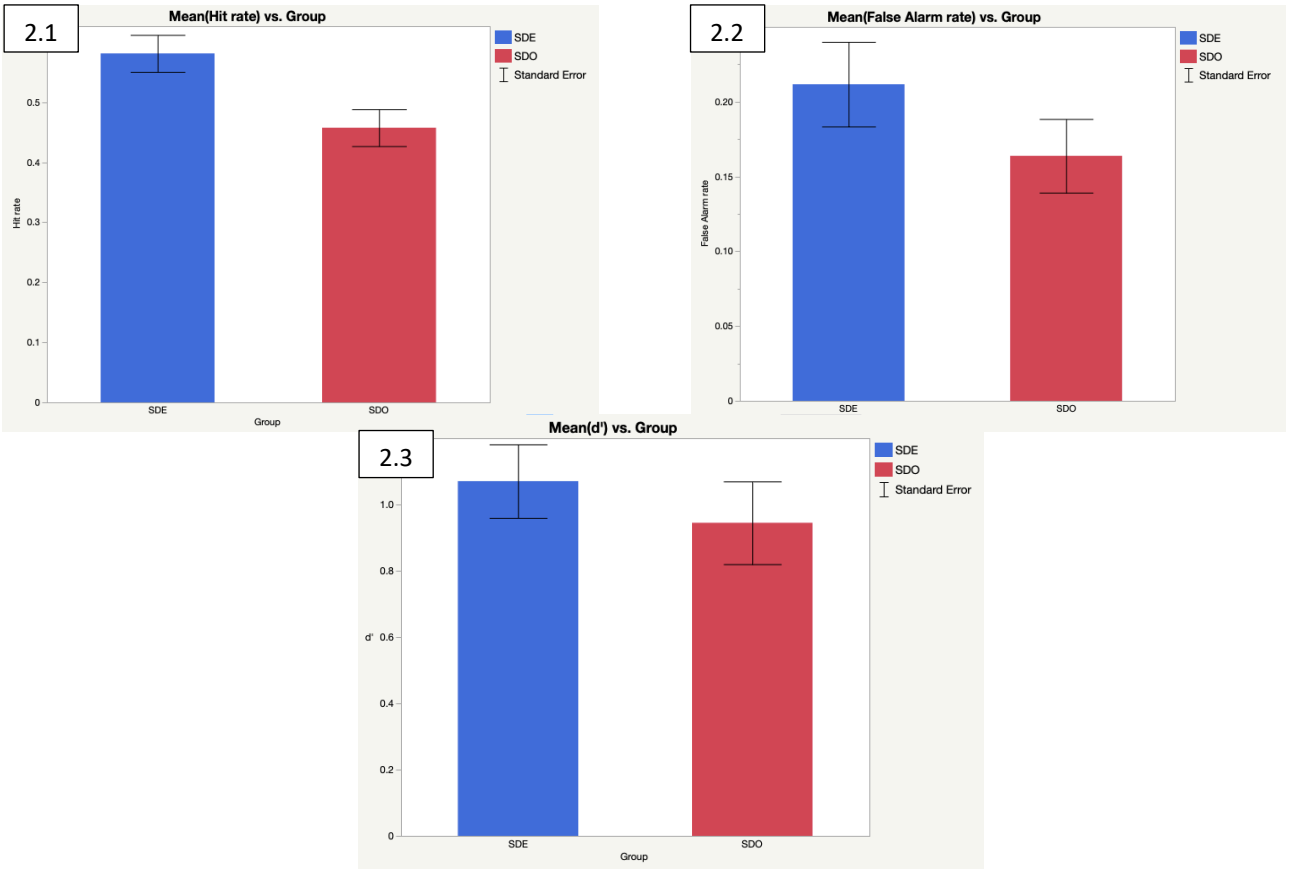
Table 3: Responses omitted, response times, and arousal ratings at encoding and/or retention. Data are presented as means and standard deviations.

	SDE	SDO	p-value
Encoding			
Responses omitted	5.71 (4.68)	5.43 (5.6)	0.885
Response time (ms)	1547.34 (217.34)	1324.07 (285.16)	0.028*
Arousal rating	2.07 (0.28)	1.95 (0.35)	0.350
Retention			
Responses omitted	1.57 (1.34)	2.07 (2.97)	0.573
Response time (ms)	1383.7 (197.34)	1318.76 (173.91)	0.364
Response time hits (ms)	1312.54 (155.71)	1314.4 (173.02)	0.976
Response time misses (ms)	1384.6 (233.97)	1283.53 (203.56)	0.234
Response time correct rejections (ms)	1317.6 (207.64)	1259.86 (199.96)	0.460
Response time false alarms (ms)	1520.07 (277.56)	1417.26 (240.8)	0.305

Results of memory outcomes

Three memory outcomes were explored as part of our memory task: the hit (hits/original images) rate, the false alarm (false alarms/distractors) rate [26] and d' [91], our primary outcome. SDE was significantly better at identifying the original images (MD [SE], -0.124 [0.044]; p=0.009), with a mean hit rate of (0.58[0.12]) compared to the SDO group (0.46[0.11]). The SDO group did slightly better at identifying the distractors although the difference was not significant (MD [SE], -0.048 [0.038]; p=0.213). The results of our primary outcome (d') also showed no significant differences between groups (MD [SE], -0.126 [0.167]; p=0.458), with the SDE group having an average d' of (1.07[0.42]) and the SDE group an average of (0.95[0.47]) (see Figures 2.1 2.2 and 2.3 for more details).

Figures 2.1, 2.2, 2.3: results for hit rates (2.1), false alarm rates (2.2) and d' (2.3)



Exploring the associations of different variables such as age, VO_2 peak, baseline cognition, fatigue, alertness, etc. and our memory outcomes did not lead to any significant results. Same can be said for subgroup analyses exploring the influence of biological sex on our outcomes. The associations between behavioral responses of the memory task and our memory outcomes showed a significant correlation between the response time at encoding and d', our primary outcome for the SDE group (R^2=0.494, p=0.005). The SDE group also showed that longer response times were associated with better hit rates and false alarm rates, though the associations for these two other memory outcomes were not significant (R^2=0.150, p=0.174) for hit rates and (R^2=0.200, p=0.111) for false alarm rates. However, when both groups were plotted together, there was a significant correlation between longer response time at encoding and better hit rates (R^2=0.262, p=0.005).

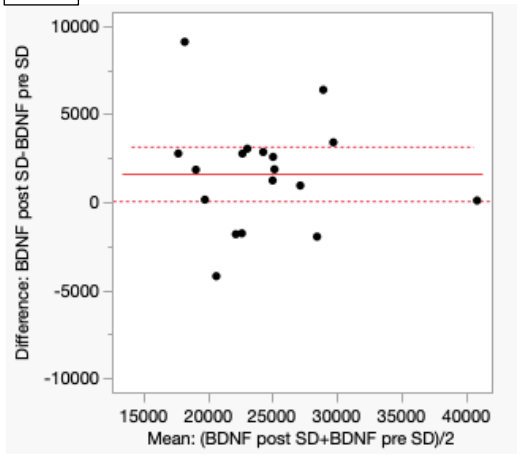
BDNF results

Our comparison of BDNF levels pre- and post-SD showed that 30 hours of SD significantly increased BDNF levels (p=0.041) (see Figure 3.1 for more details). When comparing BDNF levels at the three timepoints post-intervention using post-hoc tests, we found that exercise increased significantly BDNF levels (see Figure 3.2) compared to baseline (p=<0.0001) and that the difference immediately after exercise was significant compared to the rest intervention (p=0.002) but returned to non-significant levels after 5 and 10 minutes. The associations between BDNF levels and our memory outcomes showed that bigger AUCs were associated with better hit rates, although the correlation did not reach statistical significance (p=0.070) (see Figure 3.3). The results of our two-way (group X timepoint) ANOVA repeated measures analysis showed significant group x time interactions (F(3,49)=3.04;p=0.0375). Only the BDNF levels immediately

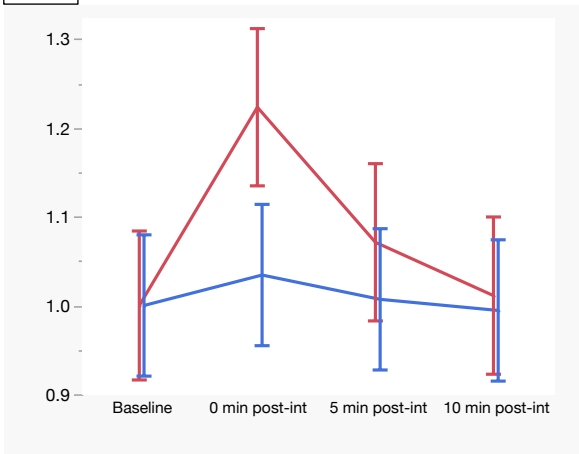
after the exercise or rest interventions reached statistical significance (MD [SE], 0.189 [0.059];p=0.0475), with higher values in the SDE group.

Figures 3.1, 3.2, 3.3: difference in BDNF levels pre- and post-SD (3.1), comparison of post-intervention BDNF levels for SDE (red) and SDO (blue) (3.2) and associations between BDNF levels and d' (blue), hit rates (red) and false alarm rates (green) (3.3)

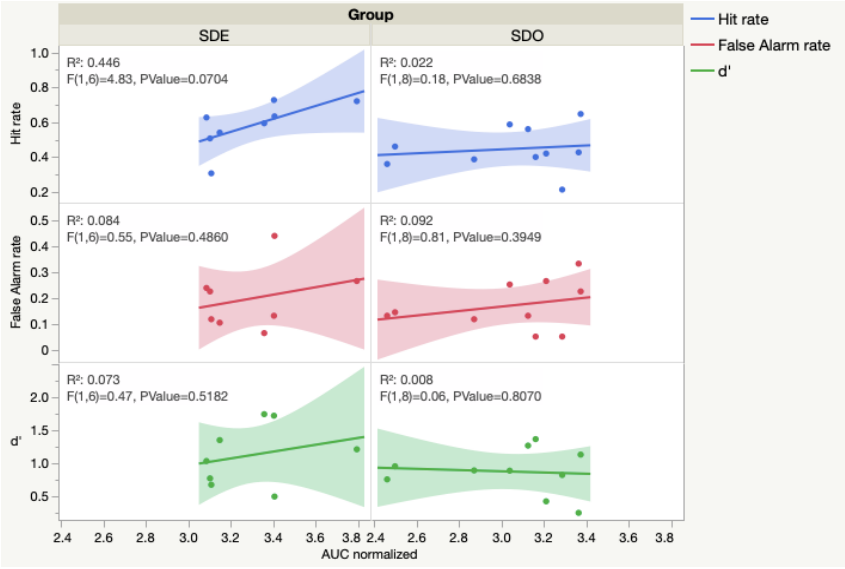
3.1



3.2



3.3



Discussion

Our study showed that an acute bout of cardiovascular exercise performed after 30 hours of SD can protect the capacity of participants to identify stimuli they have previously been exposed to (hit rate). Participants in the exercise group made more errors (false alarm rate), although this finding was not significant. When combining these two outcomes into a discrimination index (d'), the exercise group performed better but not significantly, ultimately rejecting the hypothesis that exercise would improve the capacity to discriminate between stimuli presented previously and distractors.

It could be tempting to think that the fact that both hit rates and false alarm rates were higher in the SDE group mean that participants in the SDE group simply pressed "yes" more often when presented an image and asked if they had seen it before. In the context of signal detection theory, a psychophysical approach to measuring performance that can be applied in recognition memory [98], this could be interpreted as a change of response criterion. Response criterion corresponds to the criterial level of evidence that measures whether there is a preference to determine items (in our case, images) as old or new [99]. A more conservative criterion would result in fewer hits, but also fewer false alarms whereas a more liberal criterion would result in more hits, but also in more false alarms. The middle ground would correspond to a moderate criterion, in which there is an even distribution of old and new responses. Therefore, we could attribute the results of participants in the SDE to a shift towards a more liberal criterion. However, the fact that d', which combines hit and false alarms rate, was still not-significantly better in the SDE group proved that this is not the case as they were still better able to discriminate the two and did not simply have an increase in liberal responses. There is also currently no evidence in the literature showing that sleep deprivation and/or exercise would induce a change in criterion or in

criterion noise. Furthermore, the concept of criterion variability or criterion noise itself is disputed [100]. A review and reanalysis of existing data sets by Kellen, Klauer and Singmann (2012) concluded that criterion noise as currently modeled does not have a major influence on recognition memory performance. Their results showed that most studies investigated had either no criterion noise, or low values that did not affect participants' performance [100]. It is therefore quite unlikely that our results are due exclusively to a shift in criterion.

It then remains unclear why exercise would improve an aspect of memory such as the capacity to correctly identify images that were previously shown (hit rate), but not others such as identify images introduced as distractors (false alarm rate). In addition to BDNF, exercise is known to increase the secretion of catecholamines such as epinephrine and norepinephrine [46], which are thought to play an integral role in subserving emotional memories [101]. Emotionally-charged episodic memories, influenced by the amygdala, are often more vividly recalled than more neutral memories [101]. This is believed to be partly due to the noradrenergic activity in the amygdala, which in turn modulates memory processing of brain regions including the hippocampus [102]. Previous human brain imaging studies have found that the degree of amygdala activation during encoding is highly correlated with subsequent long-term memory retention [102]. A study by Vargas et al. (2019) that investigated the selective consolidation of emotional memories in SD has shown that sleep deprived individuals showed similar recognition rates for negative emotional memories compared to a sleep control group [103]. Some studies in humans have also reported that memory is enhanced by stressful conditions that release epinephrine [102], which both exercise [46] and SD [104] are known to do. Acute exercise is thought to induce an emotionally-charged response, which can facilitate emotional memory function via exercise-induced

modulation of norepinephrine [101]. In some studies, the increase of norepinephrine measured after acquisition of stressful learning tasks strongly correlated with memory performance [105]. Considering that the SDE group had the combined stress of SD and exercise, compared to the SDO group that only had SD, the SDE had potentially increased amygdala activation that led to better memory encoding of the original stimuli [102]. It is also not unreasonable to think that since the images viewed during V2 are associated with a negatively-charged emotional experience (caused by SD [106] and the addition of exercise [101]), participants in the SDE group were able to identify them better than the images that were presented at retention (a more neutral emotional experience) and that catecholamines such as epinephrine and norepinephrine would play a role in this phenomenon. This could explain, in part, why hit rate is significantly better in the SDE group but not the false alarm rate.

However, it is important to note that most studies investigating emotional memories in humans are considering the emotions induced by the stimuli rather than the emotions related to the context in which memory was encoded [101] [102] [103]. In our experiment we chose neutral images and the arousal rating at encoding is not different between groups, the emotional component of the experience would then be more context-related rather than content-related. More studies exploring the relationship between exercise and memory during SD with an emphasis on pictures producing greater arousal instead of more neutral ones are needed. In addition, studies investigating the emotional context of participants partaking in SD and exercise, perhaps by adding questionnaires assessing mood, are also needed to further investigate the effect of exercise on neutral and/or emotional memories.

It seems like norepinephrine modulation could also play a role in the amount of false alarm rates [107]. A study by Lewandowska et al. (2018) found that in memory tasks performed later in

the day (10 hours after awakening) compared to closer to awakening (1 hour), participants responded more liberally. This resulted in higher false alarm rates, and they found a significant effect of time of the day on false alarm rates [107]. They attributed these results to the locus coeruleus-norepinephrine system, which shows a circadian rhythm that affects alertness, vigilance, attention, and decision-making [107]. The locus coeruleus is known to be activated by exercise and increase norepinephrine release [105]. In their study, the tonic mode of the locus coeruleus-norepinephrine system, which causes an increase of baseline norepinephrine release, resulted in poorer performance with increased false alarms [107]. In our case, we cannot attribute differences in false alarm rates to participants being awake for longer at encoding since SD time was standardized. When exploring the amount of time that participants had been awake for on V3 prior to retention, we observed that participants in the SDE and SDO group had also not been awake for a significantly different amount of time (MD [SE], -63.210 [85.440]; p=0.466). Furthermore, we did not find a correlation between time being awake before retention and any of the memory outcomes (hit rate, false alarm rate or d'). Therefore, the differences in false alarm rates were not due to participants being awake for longer in any stage of the memory task and might rather be related to the secreted levels of norepinephrine at encoding.

Another interesting finding of our study is the correlation that can be observed between longer response times at encoding and improved memory performance. Participants in the SDE group who took longer to respond at encoding showed significantly better memory scores (d') compared to those who took less time. When all participants were pooled together, participants that took longer to respond at encoding had better hit rates. A paper by Mograss et al. (2009) that looked at the EEG activity in relation to memory after normal sleep and SD has found that higher

vigilance levels 30 minutes before memory encoding were significantly correlated with longer reaction times to the stimuli in sleep deprived participants [108]. However, in that study, participants were told to respond as fast as possible unlike the instructions we gave to our participants. In our study, although alertness levels before encoding between groups were not different, when exploring associations between alertness (assessed by the Sleep-2-Peak®) and the response time at encoding in the SDE group, we found an almost significant correlation (R^2= 0.311, p=0.059) between higher alertness levels before encoding and longer response times. In opposition, in the SDO group, longer response times were associated with lower alertness levels, but not significantly (R^2= 0.126, p=0.284). Similar results can be observed when looking at the subjective fatigue levels before encoding (as assessed by the VAS-F) in the SDE group, where there is a non-significant association between longer response times at encoding and lower fatigue levels (R^2= 0.190, p=0.157) as opposed to (R^2= 0.077, p=0.408) in the SDO group. The EEG analysis of our results will likely provide more insight on this matter.

While many animal studies have noted a decrease of BDNF levels after SD [4], other studies in humans investigating peripheral serum BDNF levels did not observe any changes [109]. Some previous studies even saw an increase in peripheral serum BDNF levels post-SD [110] [111] which could be considered as a compensatory mechanism to maintain cognitive functions during SD. What we found in our study coincides with these latter findings, with participants having significantly greater peripheral serum BDNF levels post-SD compared to baseline (p=0.041). A study by Giacobbo et al. (2016) found elevated levels of peripheral serum BDNF in participants that underwent 24 hours of SD compared to sleep controls and concluded that the elevated BDNF levels potentially contributed to preserve prefrontal cognitive functions such as attention [110].

However, in our study we did not find associations between BDNF increases during SD and changes in alertness that could support of the hypothesis proposed by Giacobbo.

Based on previous studies [46] [51] [112] we expected to see an increase in BDNF level post-exercise intervention and higher BDNF levels to be correlated with better memory retention [46]. We indeed observed a significant increase in BDNF levels post-exercise compared to baseline ($p=<0.0001$) and compared to the rest intervention ($p=0.002$), which confirms our second hypothesis. Although not significant, ($p=0.070$), we did observe that larger BDNF AUCs were associated with better hit rates in the SDE group (see Figure 3.3). This is interesting considering that the average hit rate was the only memory outcome that was significantly different between groups. No previous study has investigated the relationship between BDNF levels and the prevalence of hit rates and/or false alarm rates in an episodic memory task. However, some studies have found that BDNF holds a role in amygdala-dependent learning [49] and is necessary for associative learning in aversive contexts [113]. Similarly to what has been previously discussed, the catecholamines secreted during exercise such as norepinephrine stimulates the amygdala which modulates memory processing and is correlated to better memory retention [102]. The elevated levels of BDNF post-exercise and the role of BDNF in amygdala-dependent learning could potentially explain why only the SDE group showed a correlation between higher BDNF levels and better recognition of the old stimuli.

Potential Problems and Limitations

The timing between the exercise or rest intervention and the beginning of the encoding of the memory task was important to monitor so that the intervention provided the right amount of stimulus without causing fatigue that could alter the results. It has been shown that an acute bout of exercise performed during SD increases alertness for a period of 20 to 50 minutes post-exercise [8]. EEG signals after 50 minutes after exercise in situation of SD have shown an increase in awake delta waves [8], which are usually seen in deep sleep [4]. After the exercise or rest intervention, we drew three blood samples at 0-, 5- and 10-minutes post-intervention. This meant that our time of alertness after exercise before witnessing potential delta waves was limited since the encoding of the memory task itself lasted 15 minutes. To ensure participants were in an optimized state to encode new memories, we opted for a window of 20 to 35 minutes post-exercise to begin the encoding of the memory task. To minimize the timing of transition from exercise to the EEG lab where the memory task took place, the EEG cap was mounted on the participant's head at 29.5 hours of SD, prior to the beginning of the exercise or rest bout.

Considering that the phase of the menstrual cycle a person is in affects their sleep duration and quality [96], the fact that we did not control or recorded the cycle's phase of our menstruating participants constitutes a potential limitation of this study. The luteal phase (the phase after ovulation before the menses) is typically associated with poorer sleep [96]. We could then assume that if the days prior to the SD protocol happened to be during the follicular phase of the menstrual cycle of the participant (the phase succeeding the menses but preceding ovulation), they might be more rested and resilient to the negative effects of SD compared to a participant in their luteal phase [96]. However, a previous study that observed alertness during SD as assessed by a psychomotor vigilance task has shown that participants in the follicular phase of their menstrual

cycle showed the poorest level of performance, while participants in their luteal phase were relatively protected from a decrease in alertness level [114]. This counterintuitive finding could possibly be explained by the increase of body temperature that happens in the luteal phase, which results in poorer sleep but also in increased wakefulness and alertness [114]. When the menstrual phase of participants in that study was unknown, it appeared as if there was a light decrease in alertness in menstruating people compared to those who do not have menses, masking the larger decrease in participants that were in their follicular phase compared to those who were in their luteal phase [114]. Not taking the phase of menstrual cycle into account while collecting our data might result in a bias in the results when comparing the data of menstruating participants (mostly females) to those of non-menstruating participants.

Another limitation to the study is the fact that the retention task did not always happen at the same time of the day as the encoding did four days prior. Participants' work/school schedules made it impossible to ensure that participants all came back at the exact time they did to avoid circadian fluctuations. However, the wake-up time window we imposed for the morning of V2 ensured that encoding always happened during the same period of the day (between 12:30 pm and 5:15pm). Fortunately, the retention task mostly happened during that time of the day as well, with only a few exceptions. In addition, average alertness levels prior to the retention task were almost identical between groups (see results for fatigue, energy, and alertness).

Conclusion

The objective of this study was to determine whether a single bout of cardiovascular exercise performed after 30 hours of SD, and before the encoding of an episodic memory task, could protect episodic memory from SD. We suggest that exercise does protect memory to a certain extent although the mechanisms remain unclear and need to be further investigated. This study is the first to investigate the protective effect of exercise on episodic memory and exploring potential neuroplasticity markers in sleep-deprived humans.

According to the National Foundation of Sleep's guidelines [115], one third of Canadians are not sleeping enough [116]. This alarming trend has profound negative impact on human health, including an increase in sickness and mortality rates [1]. In addition to insults on physical and mental health, lack of sleep has enormous societal and economical adverse outcomes. One of them is the reduction of productivity caused by an increased amount of work and/or school days missed and the reduction of the working population [1]. There are many reasons why we lack sleep from time to time, whether it is because of school/work, travelling, or to engage in social activities. When lack of sleep is unavoidable, it is valuable to know that mitigation strategies exist to limit the negative effects of SD. Exercise should not be considered as a substitution for sleep but given the current trend in sleep insufficiency [116], investigating the extent to which it could partially mitigate the negative effects of SD in the neurophysiological domain, including neuroplasticity and memory, is of enormous interest.

This goes without saying that poor sleep quality and suboptimal sleep duration have an adverse reciprocal effect on neurodegeneration and neuropsychiatric disorders such as Parkinson's disease [117] [118] and stroke [119, 120]. Impaired plasticity, caused by alterations of the normal sleep-wake cycle is thought to be involved in the onset of movement disorders such as Parkinson's

disease [117], which in turn causes sleep alterations that have been linked with an increase in cognitive decline and dementia [118]. Similar effects have been observed in people with stroke, with sleep problems increasing stroke risk [120], and creating larger deficits in cognitive performance [119].

Gaining knowledge on biomarkers of neuroplasticity susceptible to SD and understanding how they respond to exercise provides important insights for clinicians to develop targeted strategies to protect structures and functions of the brain affected by SD. Our findings could also constitute valuable information for the public, especially shift-workers, students and/or people with poorer sleep who could benefit from the addition of exercise to their regular activities to counteract the negative effects of sleep loss on their cognition, including memory.

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