

Original Research Article

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Acute partial sleep restriction attenuates working memory performance and does not affect BDNF in young adults

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Abstract

Objectives: Sleep loss decreases working memory (WM) performance in young adults. The mechanisms that regulate WM performance during sleep loss are integrative and likely depend on the duration of perturbed sleep. The aim of this research was to investigate the impact of a single night of partial sleep restriction (PSR) on WM, and the extent to which factors such as cardiorespiratory fitness and brain-derived neurotrophic factor (BDNF) influence WM performance following one night of PSR.

Methods: We measured WM performance after one night of PSR in twenty-two young adults ($n=13$ females) with otherwise normal sleep habits. Participants completed an N-back test following one night of normal sleep (6–9 h sleep duration) and after one night of PSR (3 h sleep duration). To account for learning effects due to repeated cognitive testing, a time-matched normal sleep control group was also collected ($n=22$). Plasma BDNF was measured after normal sleep and PSR. Cardiorespiratory fitness was assessed via an incremental test to exhaustion on a cycle ergometer.

Results: 3-back reaction time was slightly slower after PSR compared to the control group ($P_{\text{Interaction}}=0.038$; $\eta_p^2=0.10$). No changes in BDNF were observed between sleep conditions ($p=0.720$; *Cohen's d*=−0.04). WM performance after acute PSR was inversely related to cardiorespiratory fitness ($p=0.025$; Pearson's $r=-0.48$); and these associations were observed without changes in plasma BDNF.

Conclusions: Our data suggest that a single night of PSR may acutely impair WM in young adults and contribute to an understanding about the incipient cognitive consequences of shortened sleep.

Keywords: somnolence; brain-derived neurotrophic factor; cognitive function; reaction time

Introduction

Sleep plays a critical role in modulating cognitive function, and short sleep durations impose a profound physiological stress that adversely impacts cognition in humans. Despite the importance of continuous and adequate sleep, contemporary societal demands shorten sleep duration [1] such that almost 10 % of the global population reports sleep durations of less than 6 h per night [2]. The impact of shortened sleep on cognitive function depends on numerous factors, including sleep quality, sleep duration, and frequent insomnia symptoms [3–6]. Chronically shortened sleep associates with decreases in working memory (WM) performance, decreases in vigilance [7, 8], and increases in the risk of neurological disease [9]. Acute reductions in sleep durations, such as observed during total sleep deprivation (TSD) where sleep is eliminated for 24 h or more, also impairs both motor performance [10] and neurobehavioral performance which may increase rates of serious workplace errors [11].

Indeed, laboratory evidence demonstrates that acute TSD or partial sleep restriction (PSR) transiently impairs many aspects of cognition including WM, evidenced by decreases in accuracy on an N-back test of WM in healthy humans [12–14]. Not surprisingly, the magnitude of cognitive dysfunction increases as a function of greater accumulated sleep debt [13], such that total sleep deprivation results in exacerbated cognitive dysfunction compared to PSR across longer periods of wakefulness [14]. Indeed, total sleep deprivation represents an excellent model for investigating the deleterious physiological effects of prolonged wakefulness; however, humans

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may rarely miss an entire night of sleep. Conversely, PSR due to poor sleep hygiene and rigid lifestyle and occupational schedules is likely more common in society across longer timescales [15]. Although the negative impacts of chronic PSR on cognition are well described, the effects of acute PSR (e.g., one night of 3 h of sleep) on WM in males and females are comparatively less researched.

Factors that underlie the impaired cognition that is associated with shortened sleep may be integrative in nature. One such factor may involve changes in concentrations and signalling of the neurotrophin brain-derived neurotrophic factor (BDNF). BDNF is critical for cognitive processes including learning and memory. Further, BDNF orchestrates activity-dependent synaptic plasticity and is implicated in the regulation of sleep by increasing regional sleep pressure in activity-dependent manner during waking hours [16]. Circulating BDNF follows a biphasic response to sleep stressors, where chronic perturbations to sleep decrease concentrations of circulating BDNF, and acute total sleep deprivation increases BDNF levels [17, 18]. Increases in circulating BDNF, without the expected impairments to cognitive performance following acute total sleep deprivation, may reflect synaptic potentiation due to prolonged waking without appropriate synaptic rescaling during sleep and thereby uncouple the protective relationship between elevated circulating BDNF and cognitive performance [17]. The impact of acute PSR on circulating BDNF in healthy humans, however, remains unexplored. It is plausible that the early stress-associated elevations in circulating BDNF following sleep restriction may contribute to the preservation working memory, in accordance with the proposed adaptive response. However, domain-specific attenuations in attentional measures, which are sensitive to acute instances of PSR [13], may be impaired due to the increases in pressure to sleep prompted by BDNF [16] and decreases in vigilance characteristic of acute sleep restriction. Furthermore, adequate vascular function such as vasomotion of cerebral arterioles penetrating the brain parenchyma [19] – which may be in part facilitated by BDNF signaling [20] – is integral for sleep-dependent metabolic flux in the brain and the overall maintenance of cerebral health and cognitive function [21]. Research further indicates that maladaptive sleep causes significant perturbations to vascular function [22]. Examining associations between vascular function and WM performance during instances of restricted sleep presents an opportunity to highlight cognitive performance as the output of interactions between multiple physiological systems, all reliant on adequate sleep duration.

The objective of this study was to investigate the effect of PSR on circulating plasma BDNF and WM performance in young and healthy adults. We hypothesized that WM performance would decrease following a single night of PSR,

and that this impairment would be associated with an increase in circulating plasma BDNF compared to when measured after one night of normal sleep. The summary of this article is presented in Figure 1.

Materials and methods

This paper presents an analysis of secondary outcomes from an experiment that was designed to examine the effects of PSR on vascular function [23]. Twenty-two male and female adults between the ages of 18–35 were recruited to participate in this experiment involving one night of PSR. A parallel-arm and normal sleeping time-control group, consisting of an additional sex-matched 22 participants, was used to account for the passage of time and potential learning effects due to repeated cognitive testing. Inclusion criteria for participation were the absence of any diagnosed sleeping disorders (e.g., obstructive sleep apnea, insomnia, narcolepsy), or a history of diagnosed medical disorders including any cardiovascular, musculoskeletal, and metabolic diseases. Data from female participants in the experimental group were collected during the early follicular phase of the menstrual cycle as determined by self-report, except for one participant who reported use of an intra-uterine device. All participants provided written informed consent and all experimental procedures that were approved by the Hamilton Integrated Research Ethics Board (Project ID: 8270) and conformed to the *Declaration of Helsinki*, with the exception of preregistration.

Study protocol and data collection

To investigate the effect of acute PSR on WM and BDNF, experimental group participants completed two experimental visits consisting of normal sleep or PSR, in a fixed order. Prior to completing experimental visits, participants attended a familiarization session where they were introduced to study procedures, completed practice trials of the WM test, and completed a maximal exercise test to exhaustion on a cycle ergometer to characterize cardiorespiratory fitness (VO₂ peak test). Participants were asked to arrive to the laboratory in a standardized fasted state (within 6 h preceding the visit), without consuming caffeine or alcohol (within 12 h preceding the visit), and without performing moderate-to-vigorous physical activity (within 24 h preceding the visit).

A habitual sleep baseline period was completed prior to commencement of the first experimental condition, where participants were instructed to maintain their habitual sleep

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INTRODUCTION

Poor sleep duration and architecture impairs cognitive function in humans.



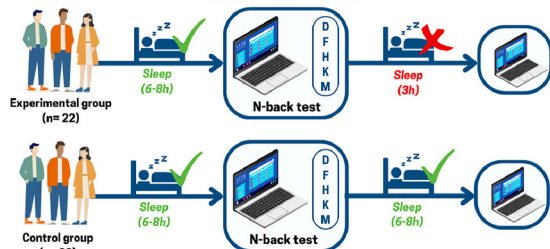
However, the effects of **one night of sleep restriction on working memory (WM)**, and the roles of cardiorespiratory fitness (**CRF**) and brain-derived neurotrophic factor (**BDNF**), remain unclear.



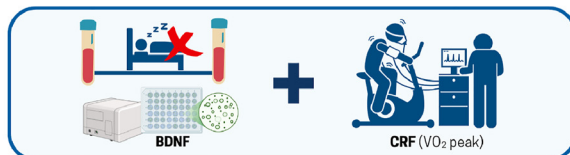
Objective: to investigate the impact of a single night of partial sleep restriction (PSR) on WM, and the extent to which CRF and BDNF might modulate this response.



METHODS

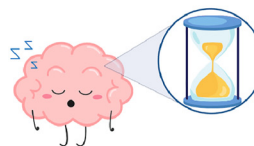


WM performance was assessed using an **N-back test** after a **normal sleep** (6–8 h) and after one night of **sleep restriction** (3 h) in the **experimental group** (n = 22), while the **control group** (n = 22) performed the **N-back tests** after two **normal nights of sleep**.



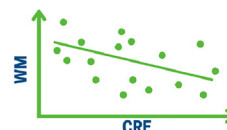
In the experimental group only, plasma **BDNF** before and after **sleep restriction** was enumerated using an **ELISA**, and **CRF** was estimated by VO_2 peak which was measured using an **incremental test to exhaustion**.

RESULTS



Reaction time was slightly **delayed** after **acute partial sleep restriction** compared to normal sleeping.

Contrary to our hypothesis, **changes in WM performance were not related** to changes in **plasma BDNF**.



Worsened WM performance after acute partial sleep restriction was **associated** with **better CRF**.

CONCLUSION

One night of partial sleep restriction may impair WM performance in healthy young adults. The magnitude of WM impairment after acute perturbations to sleep may depend on responses from integrative physiological systems.



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Figure 1: Graphical representation of this study. Key points: (1) working memory assessments were conducted using an N-back task and plasma BDNF was measured after normal sleep and after acute partial sleep restriction in order to examine the relationships between acute perturbations to sleep and circulating BDNF dynamics in humans. (2) Sleep restriction slightly reduced reaction time during the N-back task relative to a normal sleeping control group. (3) Changes in reaction time were independent of changes in plasma BDNF.

behavior for at least three nights prior to undergoing testing for the normal sleep condition. Following the normal sleep condition, all participants completed the acute PSR condition, which was one night of 3 h sleep. For PSR participants were instructed to sleep for 3 h during the second half of the night (after 02:00 h) and returned to the laboratory the next morning. All data was collected at approximately the same time in the morning or early afternoon to avoid a diurnal

influence on differences in outcome measures (NS collected at 11:12±02:02 hh:mm; PSR collected at 11:11±01:59 hh:mm). Sleep duration was recorded via an activity tracking device (Fitbit Charge HR, 2014; San Francisco, CA, USA), a mobile sleep recording application (Sleepcycle; Gothenburg, Sweden) and via a consensus sleep diary [24] that participants completed each morning during the experimental phase. In addition to sleep duration, the consensus sleep diary

includes a subjective rating of sleep quality using a Likert scale ranging from 1 (very poor quality) to 5 (very good quality).

Experimental group data collection sessions began with of 10 min of supine rest. Heart rate variability (HRV) was recorded for an additional 5 min in the supine position. After HRV acquisition, participants underwent assessment of vascular structure and function [reported elsewhere; [23]]. A venous blood sample was also collected during the vascular testing sessions. Participants assumed an upright seated position and completed the N-back test of working memory [25] after the vascular function assessment. A three-lead ECG remained connected to the participants as they completed the N-back testing to monitor HRV.

A separate time-control group was included to account for potential learning effects associated with repeated cognitive testing. The time-control group was instructed to maintain their habitual sleep duration throughout the experimental period. Participants in the time-control group attended two sessions to the laboratory where they engaged only in an identical N-back assessment of working memory as the experimental group after 15 min of supine rest. The time control was only used to assess cognitive performance. Blood samples and hemodynamic assessment was not taken from participants in the time control group.

VO₂ peak cardiopulmonary exercise test

Cardiorespiratory fitness moderates associations between sleep quality and memory performance in older adults [26]. We therefore measured VO₂ peak to characterize cardiorespiratory fitness levels in our sample of young and healthy humans. Participants in the experimental group completed a VO₂ peak to exhaustion test on a cycle ergometer during the familiarization visit. Participants were fitted with a face mask and a heart rate monitor (Model A300, Polar H9 heart rate sensor; Polar Electro Oy, Finland). Gas exchange was measured using a mixing chamber and metabolic cart (COSMED; Quark CPET). The ramp protocol involved a three-minute warmup at 50 W (W), thereafter followed by a progressive increase in resistance at a rate of 1 W every 2 s. Participants were instructed to maintain a pedaling cadence of 70–90 revolutions per minute (rpm) throughout the entire duration of the exercise test. VO₂ peak was defined as plateau in VO₂ despite an increase in work rate (W). We also defined VO₂ peak according to secondary criteria if a plateau was not achieved, including a respiratory exchange ratio (RER) ≥ 1.1, the participant reaching volitional exhaustion, or a HR within ±5 beats of their age-predicted HR maximum [27]. VO₂ peak was calculated as the average VO₂ in three 10-s

bins that occurred concomitant to the criteria for VO₂ peak and is reported relative to the participant's body weight (mL/kg/min).

N-back test of working memory

To assess working memory, both experimental and control group participants completed the 1- and 3-back variants of the N-back test of WM on a laptop computer (Inquisit, by Millisecond Software; Version 6.4.2). Prior to the commencement of each test, a researcher read a standardized description of the N-back instructions and participants performed a brief practice trial of each test variant to minimize practice effects (Supplementary Script 1). Participants completed the N-back test in a quiet room free of auditory or visual distractions and completed three iterations of the 1-back and three iterations of the 3-back in a randomized order. Letters were presented on a computer screen to the participants individually with a stimulus onset asynchrony set to 2,500 ms and a stimulus presentation time of 500 ms. The match to mismatch ratio was 1:2 for each of the six blocks, and each block consisted of 15 trials. WM performance during the N-back task was quantified using three different metrics, including (i) mean hit reaction time (RT); (ii) hit rate; and (iii) d-prime sensitivity. Each of the performance metrics were quantified separately for the 1-back condition, the 3-back condition, and for the overall N-back test.

BDNF analysis

Venous blood was sampled from the antecubital vein in a subset of 16 participants in the experimental group. Blood was drawn from participants following a period of supine rest and at the start of the data collection session both before and after acute PSR. Plasma samples were collected into 4.0 mL K2 EDTA vacutainer tubes for plasma (BD Vacutainer; Franklin Lakes, NJ, USA) and centrifuged for 15 min at 4 °C at 4,000 rpm. The plasma supernatant was collected, and all samples were stored at –80 °C until use. Plasma BDNF represents the unbound and bioavailable pool in circulation [28] and was therefore analyzed using a commercially available enzyme-linked immunoassay kit (BEK-2211-2P; Biosensis, Thebarton, SA, Australia). An independent third-party has reported the intra- and inter-assay coefficients of variation for this immunoassay kit to be 1.0 % and 5.0 %, respectively [29, 30]. Plasma BDNF enzyme-linked immunoassays and standard curves were performed as per the manufacturer's instruction.

Heart rate variability and vascular outcomes

HRV was measured to estimate cardiovagal control of heart rate and the autonomic response to acute PSR. HRV was quantified in the experimental group during supine rest and whilst seated during the N-back test after both the normal sleep and PSR data collection sessions. Participants were fitted with three-lead electrocardiography to collect continuous cardiac signals. The cardiac ECG data was recorded at a sampling frequency of 1,000 Hz for 5 min during supine rest, and during the last single minute of the N-back test after both the normal sleep and PSR data collection sessions. Only high frequency activity could be estimated from these recording durations [31]. HRV was thus represented in the time-domain as the root-mean square of successive RR intervals (RMSSD; m/s) using algorithms provided by LabChart8 Pro (ADInstruments Inc; Colorado Springs, CO, USA) analysis software. Vascular outcomes included resting hemodynamics such as heart rate and blood pressure, flow-mediated dilation at the brachial artery, and carotid-to-femoral pulse wave velocity, which estimate endothelial function and central arterial stiffness, respectively. These data were collected whilst adhering to published guidelines [32, 33], and the details pertaining to the collection of these outcomes were previously described in a derivative [34] of this experiment.

Sample size and statistical analyses

We had the capacity to detect large interaction effects ($\eta_p^2=0.192$) between condition and group for measures of WM performance; and this effect magnitude is in accordance with prior research that observed a significant decrease in N-back test performance after several nights of partial sleep restriction [13]. Using this effect along with the customary thresholds for type 1 and type 2 errors, $\alpha=0.05$ and $\beta=80\%$, we simulated experiments in the ‘Superpower’ R package [34] and found that a total of 22 participants per group allowed observation of the expected effects.

Data were treated using R version 4.3.1 [35]. A linear mixed model with fixed terms group (experimental or time-control) $\times$ time (to denote visit 1 or visit 2) interaction and participant identification as a random effect was used to compare N-back WM performance. Tukey post-hoc penalties followed significant main effects. We used a paired *t*-test to compare plasma BDNF levels before and after acute PSR in a subset of 16 participants. Exploratory analyses were conducted in this study to generate hypotheses related to mechanisms that may underlie putative changes in WM acutely following a single night of PSR. N-back performance

metrics of the experimental group were z-transformed relative to the mean and standard deviation of those metrics from the time-control group. These z-transformed performance metrics were then regressed against VO_2 peak to describe the effects of cardiorespiratory fitness on changes in WM after acute PSR relative to normal-sleeping controls. We performed further correlations to examine the extent to which changes in circulating plasma BDNF and hemodynamic parameters related to changes in WM performance parameters measured after normal sleep and acute PSR. All data represents mean $\pm$ standard deviation (SD) unless otherwise stated.

Results

Participant characteristics

Data from a total of forty-four participants ($n=22$ from the experimental group and $n=22$ from the time-control group) are included in this study. Participant characteristics are provided in Table 1. Sleep duration was significantly reduced with acute PSR in the experimental group across all modalities of assessment (Fitbit $\Delta=3.97$ h; 95% CI [2.94, 5.00], SleepCycle $\Delta=4.10$ h; 95% CI [3.53, 4.66], consensus sleep diary $\Delta=4.39$; 95% CI [4.16, 4.61]; all $p<0.001$) as per our intended experimental intervention (Table 1). Moreover, the perception of sleep quality as recorded by the consensus sleep diary significantly changed between conditions in the experimental group such that sleep quality was perceived as significantly poorer following PSR compared to NS (NS: 3.7 ± 0.7 ; PSR: 2.5 ± 1.0 arbitrary Likert scale units, $p<0.001$).

Table 1: Participant anthropometrics and sleep characteristics.

Variable			
Total sample n	44		
Experimental group	9 M/13 F		
Time control group	9 M/13 F		
Age, years	21 (3)		
BMI, kg/m ²	24.0 (3.2)		
VO_2 peak, mL/kg/min	41.3 (8.6)		
Experimental group sleep durations	NS	PSR	p-Value
Fitbit sleep duration, h	6.7 (2.3)	2.7 (0.7)	<0.001
SleepCycle sleep duration, h	6.5 (1.1)	2.4 (0.7)	<0.001
Consensus diary sleep duration, h	7.3 (0.5)	2.9 (0.4)	<0.001

NS, normal sleep; PSR, partial sleep restriction; BMI, body mass index. Data represents means ($\pm$ SD). p-values accepted as significant when $p<0.05$ using a paired *t*-test.

Working memory performance

Working memory performance scores assessed using the N-back test are presented in Table 2. We found a significant group by time interaction for the 3-back mean hit RT ($p=0.038$; $\beta=-100.46$; 95 % CI $[-192.20, -8.73]$), where the mean absolute magnitude of change in RT from Visit 1 to Visit 2 in the experimental group recorded a +36.13 ms difference (95 % CI $[-33.87, 106.13]$, $p=0.697$), and the control group recorded a mean RT -64.34 ms difference (95 % CI $[-132.15, 3.47]$, $p=0.227$; Figure 2). There was, however, no group by time interaction in the overall mean hit RT ($p=0.070$; $\beta=-41.20$; 95 % CI $[-84.49, 2.09]$), nor in the 1-back mean hit RT ($p=0.972$; $\beta=0.61$; 95 % CI $[-33.41, 34.63]$). We evaluated the overall proportion of correct responses and found no group by time interaction ($p=0.534$; $\beta=0.606$; 95 % CI $[-1.29, 2.50]$). The statistically insignificant group by time interaction persisted when analyzing the hit rate in the 1-back condition ($p=0.542$; $\beta=-0.01$; 95 % CI $[-0.05, 0.02]$) and 3-back condition ($p=0.756$; $\beta=0.01$; 95 % CI $[-0.06, 0.09]$) separately. There were no significant group by time interactions for overall d-prime scores ($p=0.666$; $\beta=0.09$; 95 % CI $[-0.30, 0.48]$), 1-back d-prime scores ($p=0.731$; $\beta=-0.08$; 95 % CI $[-0.53, 0.37]$), or 3-back d' scores ($p=0.614$; $\beta=0.14$; 95 % CI $[-0.39, 0.66]$).

Circulating plasma BDNF

Blood samples were obtained from fourteen participants in the experimental group who completed the WM tests, and blood samples were also obtained from an additional two participants who completed the sleep restriction intervention but without WM performance metrics. Some participants had completed the trial before blood samples were included in the protocol, explaining the discrepancy in the total number of participants vs. the number of participants with blood samples. Plasma BDNF failed tests of normality and were right-skewed based on positive Fisher skewness

coefficients. We therefore log-transformed the plasma BDNF data which then subsequently passed normality testing. There was no change in plasma BDNF levels following PSR compared to NS (presented on the log scale; NS: 489.01 ± 590.94 pg/mL vs. PSR: 516.58 ± 691.00 pg/mL; $p=0.720$; *Cohen's d* = -0.04; Figure 3A). Contrary to our hypothesis, changes in the impaired 3-back RT response did not relate to changes in circulating plasma BDNF ($R^2=-0.07$; $p=0.769$; Figure 3B). Further, exploratory correlation analyses revealed that there were no associations between plasma BDNF and measures of WM N-back performance metrics (Figure 3B; all $p>0.05$).

Heart rate variability responses

We evaluated HRV at rest and during the last minute of the N-back test in the experimental group as a crude estimator of cardiovagal modulation to measure potential associations between changes in HRV and WM performance after acute PSR. No differences were found in HRV metrics including RMSSD, SDRR, and high-frequency spectral power during working memory testing following PSR compared to NS (all $p>0.05$; representative exposition of RMSSD included in Table 3). No associations were found between changes in HRV measured in the time-domain and changes in 3-back RT when HRV was recorded both at rest, nor during the last minute of the N-back test (all $p>0.05$).

Exploratory associations between working memory performance, cardiorespiratory fitness, and vascular measures

We were interested to see if cardiorespiratory fitness, estimated by VO_2 peak, moderated the change in RT between conditions given prior research suggesting protective effects of cardiorespiratory fitness on WM performance during

Table 2: Working memory performance as evaluated by the N-back experimental paradigm.

	Time-control group (n=22)		Experimental group (n=22)		p-Value		
	Visit 1	Visit 2	NS	PSR	Condition	Group	Interaction
1-Back hit rate	98.8 (3.3)	96.4 (7.3)	97.6 (6.4)	96.4 (8.2)	0.072	0.725	0.542
3-Back hit rate	79.1 (14.3)	83.0 (13.6)	72.7 (16.1)	75.5 (15.9)	0.093	0.095	0.756
1-Back d-prime	4.95 (0.52)	4.67 (0.75)	4.77 (0.77)	4.56 (0.91)	0.038 ^a	0.456	0.731
3-Back d-prime	2.71 (1.10)	3.04 (1.15)	2.40 (0.94)	2.60 (1.00)	0.058	0.193	0.614
1-Back RT	579 (121)	587 (140)	630 (135)	638 (130)	0.347	0.195	0.972
3-Back RT	818 (191)	754 (133)	822 (247)	858 (249)	0.550	0.364	0.038 ^a

RT, reaction time (ms); LMEM, linear mixed effects model. Data from n=22 represent means (SD); ^aSignificantly different at $p<0.05$ using a linear mixed effects model.

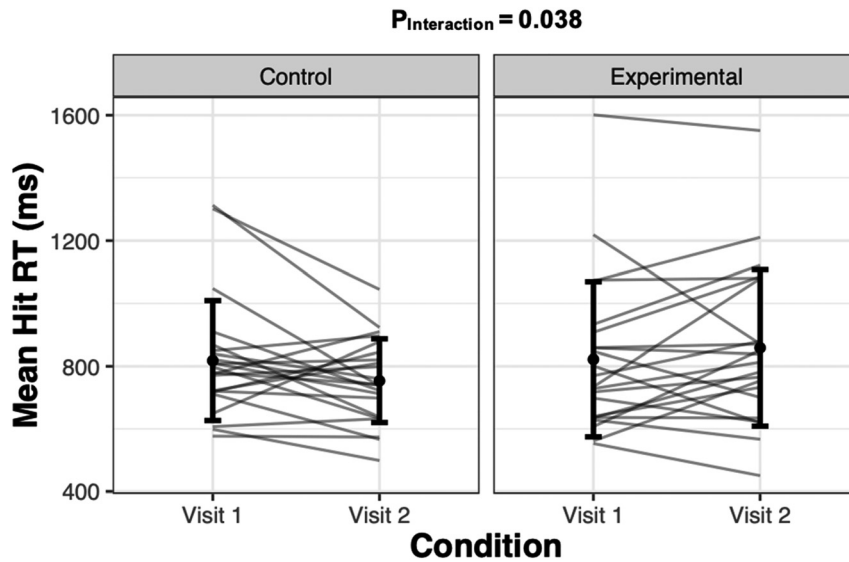


Figure 2: Mean hit reaction time (milliseconds; ms) after visit #1 and after visit #2 in the time-control group, and after normal sleep and partial sleep restriction in the experimental group. Grey lines represent individual responses, and the dot and error bars represent mean $\pm$ SD (n=22 per group).

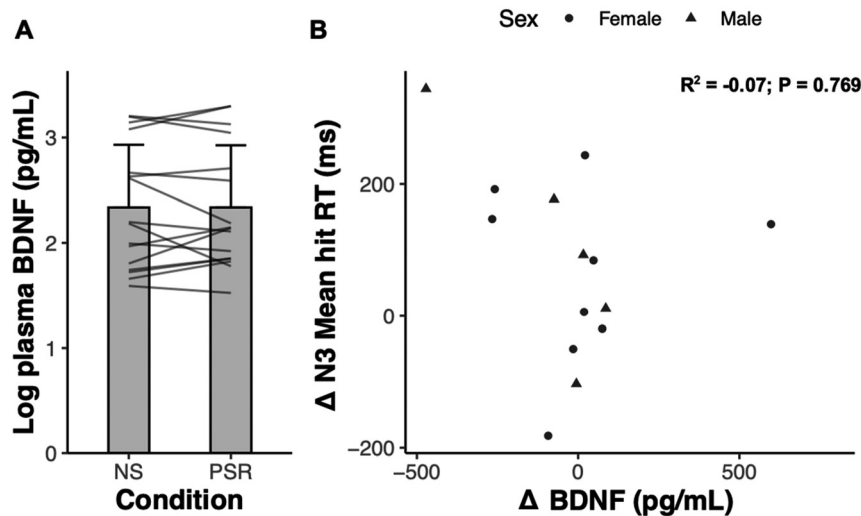


Figure 3: Plasma BDNF following normal sleep (NS) versus partial sleep restriction (PSR), and its relation to changes in working memory performance. (A) Log plasma BDNF (pg/mL) measured after NS and after acute PSR. Grey lines represent individual participant responses (n=16). Data represents mean $\pm$ SD. (B) Relationship between the change in 3-back (N3) mean hit reaction time (RT) and the change in BDNF (pg/mL) between normal sleep and acute PSR (n=14).

Table 3: Hemodynamic parameters measured after normal sleep and after acute partial sleep restriction in the experimental group.

	Normal sleep	Sleep restriction	p-Value
SBP, mmHg	113 (12)	113 (10)	0.607
DBP, mmHg	62 (6)	62 (5)	0.293
MAP, mmHg	82 (7)	81 (6)	0.365
HR, bpm	63 (10)	62 (13)	0.707
FMD (% dilation)	6.7 (3.2)	6.4 (2.9)	0.379
PWV, m/s	7.4 (1.4)	7.7 (1.4)	0.355
Resting HRV: RMSSD	62.2 (39.2)	68.4 (50.9)	0.228
N-back HRV: RMSSD	58.1 (48.7)	50.2 (33.6)	0.259

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; FMD, flow-mediated dilation; PWV, central artery pulse wave velocity; HRV, heart rate variability. Data represents means (SD).

poor sleep [26]. The standardized change in RT during the 3-back condition was regressed against VO_2 peak and, contrary to our exploratory hypothesis, we found a negative linear relationship between the standardized change in RT and VO_2 peak (Pearson's $r=-0.48$, $p=0.025$; Figure 4). This negative relationship persisted after adjusting for sex and the perceived impact of sleep restriction. Another exploratory analysis was conducted to examine associations between indices of peripheral vascular function and working memory between NS and acute PSR. No associations were detected between changes in any resting hemodynamic parameter (SBP, DBP, and HR) and measures of working memory performance (all $p>0.05$) between sleep conditions. Furthermore, no associations were found between changes in arterial stiffness estimated by pulse wave velocity and measures of working memory performance (all $p>0.05$).

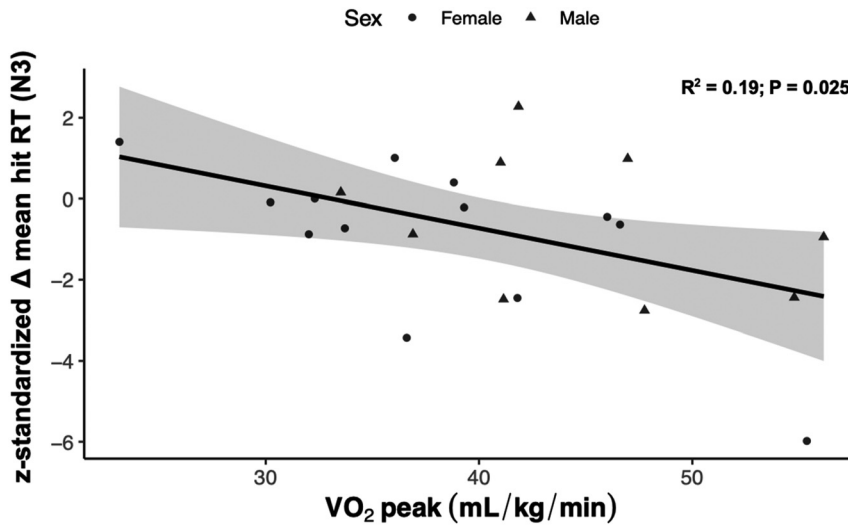


Figure 4: Correlation analysis depicting the standardized change in mean hit reaction time in the 3-back (N3) condition relative to a time-control as a function of cardiorespiratory fitness (VO_2 peak) in the experimental group ($n=22$).

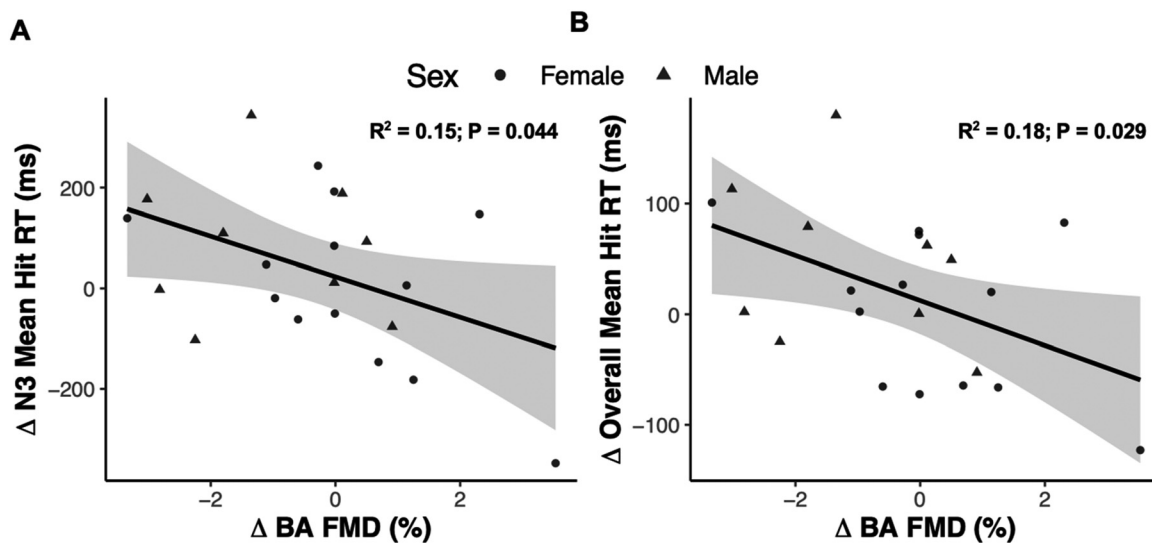


Figure 5: Correlation analysis of the association between the change in 3-back (N3) reaction time (A) and overall reaction time (B) as a function of the change in % flow-mediated dilation measured at the brachial artery (BA FMD) from the experimental group ($n=22$).

Interestingly, there was a significant negative correlation between changes in %FMD and changes in overall RT (Pearson's $r=-0.47$, 95 % CI $[-38.3, -2.3]$, $p=0.028$; Figure 5A), and changes in RT in the 3-back condition, such that larger % FMD values correlated with faster RT (Pearson's $r=-0.43$, 95 % CI $[-79.2, -1.3]$, $p=0.044$; Figure 5B).

Discussion

The purpose of this study was to investigate the impact of acute PSR on circulating plasma BDNF and WM performance in young adults. A single night of PSR acutely worsened WM

performance compared to a normal sleeping time-control group, such that there was no observed improvement due to repeated testing in the PSR group. This effect was mild in magnitude given the opposing directionality of the mean RT scores between conditions across the experimental and control groups, and did not persist following post-hoc testing. However, contrary to our hypothesis there was no effect of PSR on plasma BDNF. Interestingly, exploratory analysis revealed that higher cardiorespiratory fitness was associated with a greater decrement in WM after acute PSR. These data add to emerging findings that acute PSR may alter WM performance independent of plasma BDNF concentrations. These findings provide important insights into the

integrated physiological and neurobiological consequences of acute sleep restriction.

The observed acute and mild impairment in RT during the 3-back condition is consistent with work showing slower processing speed in females after acute PSR [36]. We add to this burgeoning body of literature by showing that acute PSR mildly impacts reaction time in both males and females. We present novel findings that changes in WM occur without changes in plasma BDNF. A shortened sleep opportunity may limit the processes underlying memory consolidation and synaptic rescaling [37]. Reduced opportunities for memory consolidation due to acute PSR may, in part, have limited the learning effects due to repeated N-back testing that ostensibly accrued overnight in the time-control group. Consistent with the active systems consolidation theory [37], synaptic rescaling during sleep reorganizes synaptic connections within and between the hippocampus and neocortex. Accordingly, acute PSR may impair consolidation of synapses created during the preceding waking period. Our data suggest, however, a mild interaction between acute PSR and WM performance given a small RT increase during the high-cognitive load 3-back task in the experimental group relative to the control group. This observation aligns with the notion that WM decrements are exacerbated as a function of accruing short sleep [14], and highlights acute PSR as a relevant, but mild cognitive stressor. Future research using an acute PSR model may therefore be guided by our findings to include larger sample sizes that are statistically powered to detect the small effects that we report herein.

The neurotrophin BDNF is critical for orchestrating synaptic plasticity and memory formation and plays an important role in regulating sleep pressure [16]. Accordingly, we assessed changes in plasma BDNF in the morning after a single night of PSR to examine the extent to which changes in circulating BDNF, particularly in a context of elevated sleep pressure, related to changes in WM. Contrary to our hypothesis, there was no change in plasma BDNF following acute PSR compared to NS. Reducing sleep to 3 h on a single night may not be a sufficient stimulus to evoke a stress-induced adaptive response. Indeed, circulating BDNF increases following acute total sleep restriction and may represent an adaptive response to protect against cognitive impairment during waking hours and increase non-rapid eye movement sleep during subsequent convalescent sleep [38]. In agreement with others [13, 36], the current experiment shows mild effects of acute PSR on WM evidenced by a slowing of response time in the 3-back condition only, which represents a higher imposed WM processing challenge. Indeed, the 1-back performance was not different from baseline, nor from the time-control group, suggesting that the effects of acute sleep loss are limited to tasks with higher

WM challenge. These results substantiate the speculation that sleep loss may first impact cellular neuronal signalling before progressing to affect broader physiological and cerebral processes as the duration of sleep restriction increases. Therefore, the impact of acute PSR on BDNF and other physiological markers may not be as pronounced as observed in more severe forms of acute sleep loss such as TSD.

Prior research indicates that higher levels of cardiorespiratory fitness may protect cognition following acute sleep deprivation [26]. Accordingly, we explored cardiorespiratory fitness as a candidate physiological factor that may buffer against impaired WM following PSR. However, we observed the opposite relationship, as higher VO_2 peak was associated with slowed RT acutely following a single night of PSR. These data suggest that individuals with higher aerobic fitness in our sample may have placed a greater emphasis on lifestyle factors, such as exercise and sleep. The disturbance to sleep caused by our intervention may have been perceived as more disruptive for these individuals, which may have influenced working memory performance via expectancy biases. Indeed, individual perceptions of sleep duration have been shown to modulate RT, independent of objectively measured sleep duration [39]. However, the negative relationship between VO_2 peak and WM RT was not impacted when we controlled for sleep perceptions in our sample. Future research may build on this exploratory finding to determine the extent to which the perceptions of sleep loss and associated expectancy biases modulate WM performance, particularly in individuals with high aerobic capacities.

We also explored the relationship between peripheral vascular function and cognition, as previous research indicates that vasomotion in the cerebral vasculature affects metabolic clearance from the brain during sleep [40]. We regressed changes in vascular endothelial cell function against changes in 3-back RT between sleep conditions and found that increased vascular function was associated with faster 3-back RT. Although exploratory, this preliminary result is conceptually consistent with importance of vascular dynamics for facilitating the flow and clearance of metabolic waste throughout the brain parenchyma during sleep [19]. A responsive endothelium, as inferred by improved conduit artery vasodilation following hyperemia, may confer a more robust cerebrovascular oscillation and therefore enhance clearance. This result, however, is exploratory and the associations between peripheral and cerebral endothelial function that are required to support this hypothesis are not yet sufficiently established [41].

Among the strengths of this study include the ecological relevance of the study design wherein sleep restriction

occurred in free-living conditions familiar to participants. This enabled participants to partake in behaviours intrinsic to their daily routines within conditions, in contrast to the constrained array of activities inherent in a supervised sleep restriction setting. Furthermore, the N-back task was used to assess a spectrum of imposed cognitive processing demands that spanned from easier processing loads (1-back condition) to comparatively difficult processing loads (3-back condition) in a randomized order. That a discernable impairment in RT was observed in the 3-back condition underscores the discriminative capacity of the N-back task in delineating nuanced cognitive impairment.

Limitations of this experiment also warrant acknowledgment. First, BDNF has been proposed to follow a biphasic pattern such that circulating concentrations of BDNF increase concomitantly with the acute stressor, and then dissipate during the sleep opportunity [17, 18]. A nighttime measure of circulating BDNF during the sleep restriction period, while sleep pressure is building, would increase the temporal resolution of circulating BDNF levels and therefore provide a better index of the integrative stress that acute PSR imposed on the body. Second, we reconciled the observed impairment in RT by deferring to reductions in opportunities for active systems consolidation and synaptic rescaling. That our current study had no direct measures of either encephalography or synaptic scaling as a proxy for consolidation limits our mechanistic speculation and presents an intriguing opportunity for further research. Objective measures of sleep quality, such as polysomnography, may have also provided insight into sleep architecture and learning that was not captured with the subjective and objective methods used to measure sleep duration herein. Measures of sleep architecture during partial sleep would provide powerful evidence to substantiate the observed effects of acute PSR on WM to extend our findings. Outcomes involving the proportion of time spent in REM sleep, and the slow-wave amplitudes characteristic of NREM, should be described in subsequent PSR interventions. Sex differences in WM performance following acute PSR have not been investigated. Our research was underpowered to detect potential sex differences, however equal representation of sexes was included in each group and sensitivity analyses with participants separated by sex did not indicate that results would differ between sexes.

Conclusions

Acute PSR yielded a mild impairment to RT relative to a time-matched and normal sleeping control on the N-back test of WM independent of BDNF changes between NS and acute PSR. The subtle effects of PSR on RT observed in our data have

broad implications for public health messaging given the prevalence of PSR, and highlights sleep duration as a relevant consideration prior to the assessment of WM in future investigations particularly where anticipated effects may be small. Furthermore, the slower RT response occurred in the absence of changes in plasma BDNF. Our exploratory analyses warrant follow-up experiments that measure integrative mechanisms, such as cardiorespiratory fitness and hemodynamic function, which may contribute to changes in cognitive processing during perturbed sleep. Our research characterizing the effects of acute PSR on WM performance and plasma BDNF levels in young adults contributes valuable insight into our understanding about the immediate consequences of short-term sleep insufficiency.

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Informed consent: All participants provided written informed consent.

Author contributions: JJW, MJM, and JMC designed the study. JMC, DW, JS, and LN collected data. JMC and JJW treated the data, interpreted results, and drafted the manuscript.

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