Received: 18 August 2023 | Revised: 6 December 2023 | Accepted: 22 December 2023

DOI: 10.1111/jsr.14145

RESEARCH ARTICLE

The effects of partial sleep restriction and subsequent caffeine ingestion on neurovascular coupling

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Summary

Habitual poor sleep is associated with cerebrovascular disease. Acute sleep deprivation alters the ability to match brain blood flow to metabolism (neurovascular coupling [NVC]) but it is not known how partial sleep restriction affects NVC. When rested, caffeine disrupts NVC, but its effects in the sleep-restricted state are unknown. The purpose of this study was therefore to investigate the effects of partial sleep restriction and subsequent caffeine ingestion on NVC. A total of 17 adults (mean [standard deviation] age 27 [5] years, nine females) completed three separate overnight conditions with morning supplementation: habitual sleep plus placebo (Norm_Pl), habitual sleep plus caffeine (Norm_Caf), and partial (50% habitual sleep) restriction plus caffeine (PSR_Caf). NVC responses were quantified as blood velocity through the posterior (PCAv) and middle (MCAv) cerebral arteries using transcranial Doppler ultrasound during a visual search task and cognitive function tests, respectively. NVC was assessed the evening before and twice the morning after each sleep condition—before and 1-h after caffeine ingestion. NVC responses as a percentage increase in PCAv and MCAv from resting baseline were not different at any timepoint, across all conditions ($p > 0.053$). MCAv at baseline, and PCAv at baseline, peak, and total area under the curve were lower 1-h after caffeine in both Norm_Caf and PSR_Caf as compared to Norm_Pl ($p < 0.05$), with no difference between Norm_Caf and PSR_Caf ($p > 0.14$). In conclusion, NVC was unaltered after 50% sleep loss, and caffeine did not modify the magnitude of the response in the rested or sleep-deprived state. Future research should explore how habitual poor sleep affects cerebrovascular function.

KEYWORDS
caffeine, cerebrovascular function, NVC, sleep restriction

1 | INTRODUCTION

Habitual poor sleep is associated with cerebrovascular disease and dementia (Wu et al., 2018), independent of other confounding illnesses (Sterniczuk et al., 2013). This relationship is concerning because a quarter of adults may fail to routinely meet the recommended 7–9 h of sleep per night (Kocevska et al., 2021).

Most research exploring the relationship between habitual sleep and cerebrovascular outcomes have focused on patients with obstructive sleep apnea (OSA), a disorder involving periods of interrupted

breathing during sleep and therefore poor quality, fragmented sleep. Research in these patient populations have reported an increased risk of dementia (Shi et al., 2018), chronically lower resting cerebral blood flow, both during sleep and wakefulness (Durgan & Bryan Jr, 2012), and impaired cerebrovascular reactivity (Reichmuth et al., 2009) compared to patients without OSA. Furthermore, in participants without OSA, studies have shown that 1 night of restricting sleep to 4 h decreases baseline cerebral blood flow (Poudel et al., 2012) and that the diurnal variation in cerebrovascular reactivity is associated with both sleep efficiency and sleep duration (Shariffi et al., 2023). Collectively, these studies suggest a role for sleep in cerebrovascular function.

The precise temporal and spatial matching of cerebral perfusion to changes in cerebral metabolism, termed neurovascular coupling (NVC), is a fundamental component of cerebrovascular function (Squair et al., 2020). Alterations in NVC are observed in dementia (Shabir et al., 2018) and may also have a pathophysiological role in preceding the disease (Zhu et al., 2022). It has been recently hypothesised that alterations in NVC due to habitual poor sleep might contribute to the increase in dementia risk, and that the chronic association of life-long poor sleep and dementia may be related to the repeated, acute exposure of sleep loss (Kapadia et al., 2020). At present, only one study has assessed the relationship between sleep and NVC in healthy human participants and observed that NVC is altered after 24 h of sleep deprivation (Csipo et al., 2021). However, no study to date has considered the effects of 1 night of partial sleep restriction on NVC, which might be more reflective of typical sleep loss.

Morning caffeine consumption in the form of coffee and/or tea is typical of Western diet, particularly after sleep loss. Importantly, a 'J-shaped' association exists between coffee intake and future cerebrovascular disease incidence (Wu et al., 2017). Despite the positive effect caffeine has on cognitive functions (McLellan et al., 2016), caffeine acutely decreases resting cerebral blood flow (Addicott et al., 2009; Field et al., 2003). This reduction in blood flow in turn causes an 'uncoupling' between cerebral blood flow and metabolism (Chen & Parrish, 2009). However, it is currently unknown how caffeine affects NVC in the sleep restricted state.

In light of the above, the purpose of this study was to investigate: (i) the impact of 1 night of partial sleep restriction on NVC, and (ii) whether caffeine ingestion affects NVC after partial sleep restriction. It was hypothesised that partial sleep restriction would alter the magnitude of the NVC response (Csipo et al., 2021), and that this relationship would be further altered by caffeine ingestion.

2 | METHODS

2.1 | Ethical approval and participants

The study was approved by the University of Exeter Sport and Health Sciences Ethics Committee (2021-M-27) and conformed to all standards set by the Declaration of Helsinki, apart from registration in a database. Written informed consent was provided prior to participation in the study. A total of 18 participants volunteered to take part; however, one participant dropped out due to moving away from the study area, therefore only 17 participants completed the study. Participant characteristics are presented in Table 1.

Exclusion criterion included being a 'poor sleeper', and was identified at three levels: a health screening form identifying diagnosed sleep disorders such as OSA, restless leg syndrome and insomnia; scoring >5/21 (where a lower score equates to better sleep), and/or reporting a normal sleep duration of ≤6.5 h on the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989); and achieving ≤6.5 h of sleep per night during the habitual sleep assessment. Volunteers were also excluded if they had any mental health issue where symptoms could be exacerbated following sleep loss (Babson et al., 2010), and/or habitually consumed >600 mg caffeine/day as participants were required to abstain from caffeine for >24 h (Rogers et al., 2005). Other exclusion criteria included current metabolic, cardiovascular, or cerebrovascular disease, known to affect NVC at baseline (Girouard & Iadecola, 2006; Maeda et al., 1993) and/or taking supplements or medication known to influence blood vessel function or blood pressure, and individuals outside of the age range (18–41 years).

2.2 | Experimental overview

Participants visited the laboratory on a total of seven occasions. This consisted of one familiarisation visit and three experimental trials. Each experimental trial required two visits, one in the late afternoon/evening, and one the following morning (Figure 1). The sleep protocol took place at the participant's own home. The study followed a repeated measures design, in order to explore the effects of: (i) normal sleep + placebo (NORM_PL), (ii) normal sleep + caffeine (NORM_Caf), and (iii) partial sleep restriction + caffeine (PSR_Caf), on NVC and cognitive function.

2.3 | Visit 1: Familiarisation

Participants were familiarised to the testing procedures ahead of completing the experimental trials. Body mass (Hampel, XWM-150 K, Hampel Electronics Co., Chung Ho City, Taiwan) and stature (Seca,

TABLE 1 The characteristics of the 17 participants (nine females).

Characteristic	Mean (SD)	Range
Age, years	27.5 (5.7)	20.4–40.3
BMI, kg/m^2	25.9 (4.7)	18.5–37.3
Habitual caffeine consumption, mg/day	178 (143)	0–462
PSQI habitual sleep duration, h/night	8.0 (0.6)	7.0–9.0
PSQI score	3 (1)	1–5
Sleep diary habitual average sleep duration, h/night	8.4 (0.5)	7.2–9.3

Note: results are expressed as mean (± standard deviation [SD]).
Abbreviations: BMI, body mass index; PSQI, Pittsburgh Sleep Quality Index.

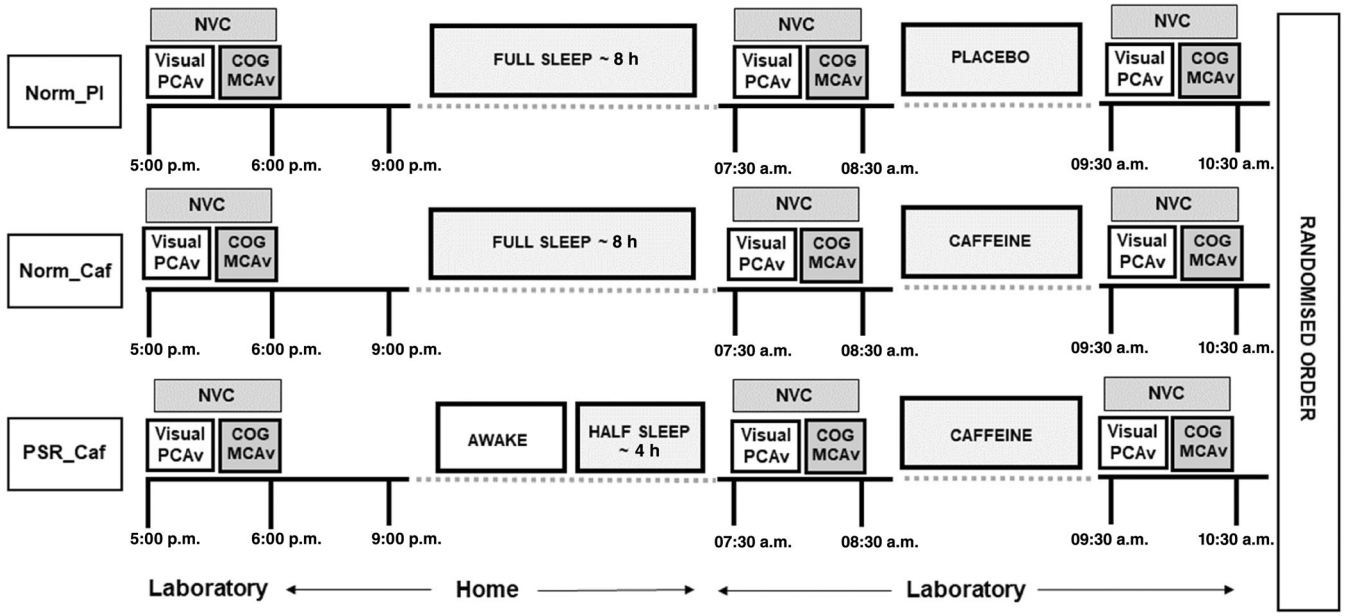

FIGURE 1 A schematic depicting the experimental trials. COG MCAv, cognitive function tests with middle cerebral artery insonated; Norm_Caf, normal sleep + caffeine; Norm_Pl, normal sleep + placebo; NVC, neurovascular coupling; Visual PCAv, visual search task with posterior cerebral artery insonated; PSR_Caf, partial sleep restriction + caffeine.

stadiometer, SEC-225, Seca, Hamburg, Germany) were measured using standard procedures, and body mass index was calculated.

Subjective sleep duration and quality were assessed during this visit using the PSQI (Buysse et al., 1989). These data were not used to prescribe sleep duration/timing during the experimental visits and was only utilised for identifying exclusion criteria and as a descriptive characteristic. Participants were instructed to complete a sleep diary across 3 consecutive nights of their typical, habitual sleep. These data were analysed to determine the sleep duration and timing for the experimental visits, so that participants kept their normal wake time.

2.4 | Visits two to seven: experimental trials

The experimental trials were completed in a randomised, counterbalanced order, with six possible orders of completion (with the original 18 participants counterbalanced across the six possible orders) and were separated by a mean (standard deviation [SD]) of 13 (7) days. For conditions where PSR_Caf was not the final trial, at least 6 days (mean [SD] 15 [10] days) separated the PSR_Caf and subsequent trial, to allow sufficient recovery sleep between trials. All trials took place in a quiet, temperature controlled (~23°C) room.

Participants arrived at the laboratory for the evening visit at a consistent time between 4:00 and 7:00 p.m. (Figure 1). Upon arrival, participants confirmed that they had met the prerequisites of the study: no caffeine consumed on the day of the visit, no food or drink (asides from water) consumed in the 2 h prior to arrival, no exercise in the 6 h prior to the visit (Burma, Macaulay, et al., 2021), and a good sleep the night before. NVC was then assessed, before the participants were sent home to complete their sleep condition. Participants were then told their target sleep onset and wake up times, which were calculated from the habitual sleep assessment. Timings were the same for the two normal sleep conditions. The target sleep onset time for PSR_Caf was calculated as the halfway point between normal sleep onset and normal wake time, resulting in a 50% sleep restriction. For example, a participant who typically slept 12:00–8:00 a.m. would have a target sleep onset and wake time of 4:00 and 8:00 a.m., respectively. During the night of the PSR_Caf trial, participants were instructed to remain mostly sedentary and refrain from eating during the period in which they would normally be asleep. For all conditions, participants were given a combined triaxial accelerometer and electrocardiogram device (Actiheart, Camntech Fenstanton, UK) to wear at night. This data was exported via the Actiheart software (Version 5.1.10) to produce estimations of sleep duration and sleep stages. Participants also recorded their sleep onset time, approximate time to fall asleep and time of waking, along with any other notes about their sleep using a sleep diary.

Participants were reminded to refrain from exercising between the evening and morning visit, as well as from consuming caffeine or alcohol. A food diary was completed during the first experimental visit to allow participants to replicate their evening meal for subsequent trials.

Participants returned to the laboratory in a fasted state at the same time across each of the conditions, within 1 h of their normal waking time (range 6:20–9:30 a.m.). Participants confirmed that they were awake during the PSR_Caf condition by sending an email every 30 min. Participants also confirmed whether they achieved a normal sleep in the Norm_Pl and Norm_Caf conditions. On one occasion, after completing the evening visit, one participant reported an abnormally bad night of sleep during a normal sleep condition, and

therefore the whole trial was completed on another occasion. The full NVC protocol was then repeated. After completing the final test, participants were provided with either 150 mg caffeine (Sigma-Aldrich, Gillingham, UK) in the Norm_Caf and PSR_Caf conditions or placebo (10 mg maltodextrin; Bulk, Lancaster, UK) in the Norm_Pl condition in pill form. Participants were blinded to the contents of the pill, and although the study was only single blind, data were saved in a manner to allow for analysis blinded to the pill. At 1 h after ingestion, approximately when caffeine peaks in the bloodstream (Nurminen et al., 1999), participants again completed the NVC tests. During the 1 h break, participants sat quietly and were limited to light desk work.

2.5 | Experimental measures

2.5.1 | Instrumentation

Transcranial Doppler ultrasound (TCD) (DWL, Compumedics, Freiberg, Germany) was used to assess blood velocity in the posterior cerebral artery (PCAv) during a series of visual search tasks, and middle cerebral artery (MCAv) throughout the cognitive function tests. A 2-MHz probe was placed over the temporal acoustic windows to acquire the cerebral blood velocity in the vessel of interest, using previously described guidelines (Willie et al., 2011), and secured in place using an adjustable headset (DiaMon, DWL). Beat-by-beat fingertip blood pressure was continuously monitored throughout the NVC assessment by finger plethysmography and quantified as mean arterial pressure (MAP) (NIBP, ADInstruments, Colorado Springs, CO, USA). All data was recorded using the LabChart 8 software (ADInstruments) and was exported at 1 Hz.

2.5.2 | Neurovascular coupling and cognitive function assessments

The NVC response was assessed with two different protocols. With the PCA insonated, NVC responses were quantified using a complex visual search task ('Where's Wally'), which provides a robust and reliable PCAv challenge with high signal-to-noise ratio (Smirl et al., 2016). This test is able to provide a surrogate measure of NVC due to the patterns of deactivation/activation evoked by visual stimuli in the visual processing areas of the brain, with regional increases in cerebral blood velocity primarily reflected in the PCA (Zaletel et al., 2004). After a 1 min resting baseline with eyes closed, participants completed at least five alternating cycles of 20-s eyes closed and 40-s eyes open to the visual stimulus (Burma et al., 2022). The Where's Wally books were positioned ~60 cm from the participants whilst they continuously searched for the characters. To account for any potential task engagement differences between trials, e.g., after sleep restriction, participants rated their level of engagement on a scale of 1–10, where 10 was 'I couldn't be more engaged in the task' and 1 was 'I could not concentrate at all on the task at hand' (Burma, Wassmuth, et al., 2021).

The NVC response was also quantified during a battery of cognitive function tests by considering the MCAv response. A 30-s resting baseline was recorded prior to each of the tests. The international shopping list test (Lim et al., 2009) was used as an assessment of working memory with an initial test in the evening, and then a follow-up test in the morning to measure overnight recall. The N-back test (2-back) was also used as a measure of working memory (Owen et al., 2005), and a 60 s modified version of the Stroop test (Bélanger et al., 2010; Stroop, 1992) for the assessment of executive function (Peterson et al., 1999). Participants also completed a 90 s go/no-go visual reaction test as a measure of inhibitory control and visual processing speed.

2.5.3 | Neurovascular coupling data handling

All cerebral blood velocity data were collected at 200 Hz using an analogue to digital converter (PowerLab, ADInstruments) and stored for offline analysis using commercially available software (LabChart 8). Data were re-sampled at 1 Hz and exported to Microsoft Excel (Version 2201) for subsequent handling.

All PCAv cycles were visually inspected for artefacts, time aligned and averaged to create one response per time point, per condition, per participant. In cases during data collection where suboptimal PCAv signals were recorded throughout single eyes-closed and eyes-open cycles resulting in subsequent adjustment of the probe to acquire a better signal, these specific cycles were excluded from analyses (Smirl et al., 2016). This resulted in a total of 29/182 cycles removed. The final 5 s of eyes-closed was averaged to create a 'baseline' value. Peak PCAv was identified as the highest PCAv value during eyes-open, and time until peak PCAv from eyes-open onset was reported. The percentage change from baseline to peak PCAv was also calculated (%ΔPCAv-peak). Total and incremental area under the curve (tAUC and iAUC, respectively) were calculated using the trapezium rule in Prism (GraphPad Software, San Diego, CA, USA, Version 9.1.2) as an index of total activation, and the iAUC was determined as the hyperaemic curve versus time above baseline PCAv. Calculating the iAUC in this way minimises the effects of any trial-to-trial baseline variation.

For MCAv data during cognitive function tests, a baseline was calculated by averaging MCAv across the 30-s baseline period. Each test was analysed in isolation and any obvious errant data points (caused by i.e., sudden probe movement) were removed before analysis. The MCAv was averaged across the test duration, and baseline MCAv was subtracted from the test average to calculate a percentage change score.

2.6 | Statistical analyses

Data are presented as means (± SD). All data were analysed using the Statistical Package for the Social Sciences (SPSS®), version 28.0.1.11 (IBM Corp., Armonk, NY, USA). Assumptions of sphericity and normality were checked using Mauchly's and the Shapiro–Wilk

TABLE 2 Sleep outcomes across the experimental trials.

Variable, mean (SD)	Norm_Pl	Norm_Caf	PSR_Caf	Trial p (η_p^2)
Estimated total sleep time, h:min	8:25 (0:40)[a]	8:08 (1:00)[a]	4:27 (1:10)	<0.001 (0.806)
Estimated time in light sleep, h:min	3:24 (1:10)[a]	3:12 (1:01)[a]	1:44 (1:02)	<0.001 (0.665)
Estimated time in deep sleep, h:min	2:17 (0:26)[a]	2:15 (0:18)[a]	1:07 (0:16)	<0.001 (0.860)
Estimated time in REM sleep, h:min	2:23 (0:44)[a]	2:29 (0:41)[a]	1:11 (0:36)	<0.001 (0.669)

Note: data are presented as mean (± standard deviation [SD]). Total number of participants 17 (nine females) for estimated total sleep time based upon data from sleep diary. Total number of participants 12 (six females) for sleep staging Actiheart data, due to loss of Actiheart data.
Abbreviations: Norm_Pl, normal sleep plus placebo condition; Norm_Caf, normal sleep plus caffeine condition; PSR_Caf, partial sleep restriction plus caffeine condition; REM, rapid eye movement.
[a]Denotes significant difference from PSR_Caf.

tests, respectively. Differences in sleep outcomes were explored using a series of separate one-way analysis of variance (ANOVA) tests. Differences in cerebrovascular and cognitive responses during each of the experimental trials were explored using a mixed model ANOVA, with condition (Norm_Pl, Norm_Caf, PSR_Caf) and time (evening, baseline morning, morning 1 h after caffeine) as the independent variables. The relationship between %ΔPCAv-peak and the MAP at PCAv-peak was assessed using Pearson's correlation. Fisher's least significant difference test was used for post hoc pairwise comparisons. The confounding effect of sex was considered in the original ANOVA model. Sex never altered the time by trial interaction ($p \geq 0.07$, partial eta squared (η_p^2) ≤0.132) therefore data for males and females were pooled. Statistical significance was accepted when $p < 0.05$, and effect sizes were calculated to determine the magnitude of any differences. Effect sizes (η_p^2) were interpreted as small (<0.06), moderate (0.06–0.14) and large (>0.14) for ANOVA analyses and as small (≥0.2 – <0.5), moderate (≥0.5 – <0.8) and large (≥0.8) for pairwise comparisons (Cohen, 1988). Data are presented as mean differences (MDs) and 95% confidence intervals (CI) unless otherwise stated.

3 | RESULTS

3.1 | Sleep outcomes

The sleep interventions were adhered to, as confirmed verbally by participants during the morning visit, and the sleep diary and Actiheart data. Table 2 shows the sleep diary and Actiheart sleep data from each of the experimental trials. By design, time of sleep onset was significantly later in the PSR_Caf trial, as compared to the Norm_Pl and Norm_Caf trials, whilst time of waking remained constant.

3.2 | Neurovascular coupling outcomes

Participant engagement during the visual search task displayed a trial by time interaction ($F = 4.712$, $P = 0.002$, $\eta_p^2 = 0.227$), with engagement significantly lower during the morning measure after PSR_Caf as compared to NORM_PL (MD = −0.7 arbitrary units (AU), 95% CI −1.3 to −0.1; $p = 0.016$, $d = 0.60$) and NORM_Caf (MD = −0.7 AU, 95% CI −1.2 to −0.2; $p = 0.012$, $d = 0.58$), with no differences apparent after pill ingestion.

3.2.1 | The PCAv during visual search task

The %ΔPCAv-peak was not related to the percentage change in MAP from baseline to the time at which PCAv peak occurred ($r = 0.015$, $p = 0.936$), therefore PCAv outcomes were not normalised for MAP.

The PCAv outcomes were never altered by the sleep condition (Figure 2). However, differences were observed after caffeine ingestion, irrespective of the sleep condition. From before to after pill ingestion, PCAv baseline significantly decreased in both the Norm_Caf (MD −4.7 cm/s, 95% CI −7.2 to −2.2; $p < 0.001$, $d = 0.70$) and PSR_Caf (MD −4.1 cm/s, CI −6.0 to −2.2; $p < 0.001$, $d = 0.67$) conditions, but was unchanged after placebo (MD +0.7 cm/s, 95% CI −1.1 to 2.4; $p = 0.985$, $d = 0.10$) (Figure 2a).

At 1 h after pill ingestion, the PCAv baseline was significantly lower in Norm_Caf (MD −3.4 cm/s, 95% CI −6.3 to −0.5; $p = 0.024$, $d = 0.55$) and PSR_Caf (MD −4.5 cm/s, 95% CI −7.0 to −1.9; $p = 0.002$, $d = 0.69$) compared to Norm_Pl (Figure 2a).

The PCAv peak significantly decreased after caffeine in both the Norm_Caf (MD −5.1 cm/s, 95% CI −8.3 to −2.0; $p = 0.001$, $d = 0.71$) and PSR_Caf (MD −5.2 cm/s, 95% CI −9.4 to −1.1; $p = 0.016$, $d = 0.54$) conditions, but was unchanged after placebo (MD +0.4 cm/s, 95% CI −1.6 to 2.4; $p = 0.660$, $d = 0.04$) (Figure 2b).

At 1 h after pill ingestion, the PCAv peak was lower in Norm_Caf (MD −4.6 cm/s, 95% CI −8.5 to −0.7; $p = 0.023$, $d = 0.55$) and PSR_Caf (MD −6.7 cm/s, 95% CI −10.1 to −3.4; $p < 0.001$, $d = 0.70$) compared to Norm_Pl (Figure 2b).

The tAUC significantly decreased after caffeine ingestion in both the Norm_Caf (MD −124.0 cm/s/30 s, 95% CI −201.8 to −46.2; $p = 0.004$, $d = 0.63$) and PSR_Caf (MD −117.4 cm/s/30 s, 95% CI −222.5 to −12.2; $p = 0.031$, $d = 0.48$) conditions, but was unchanged

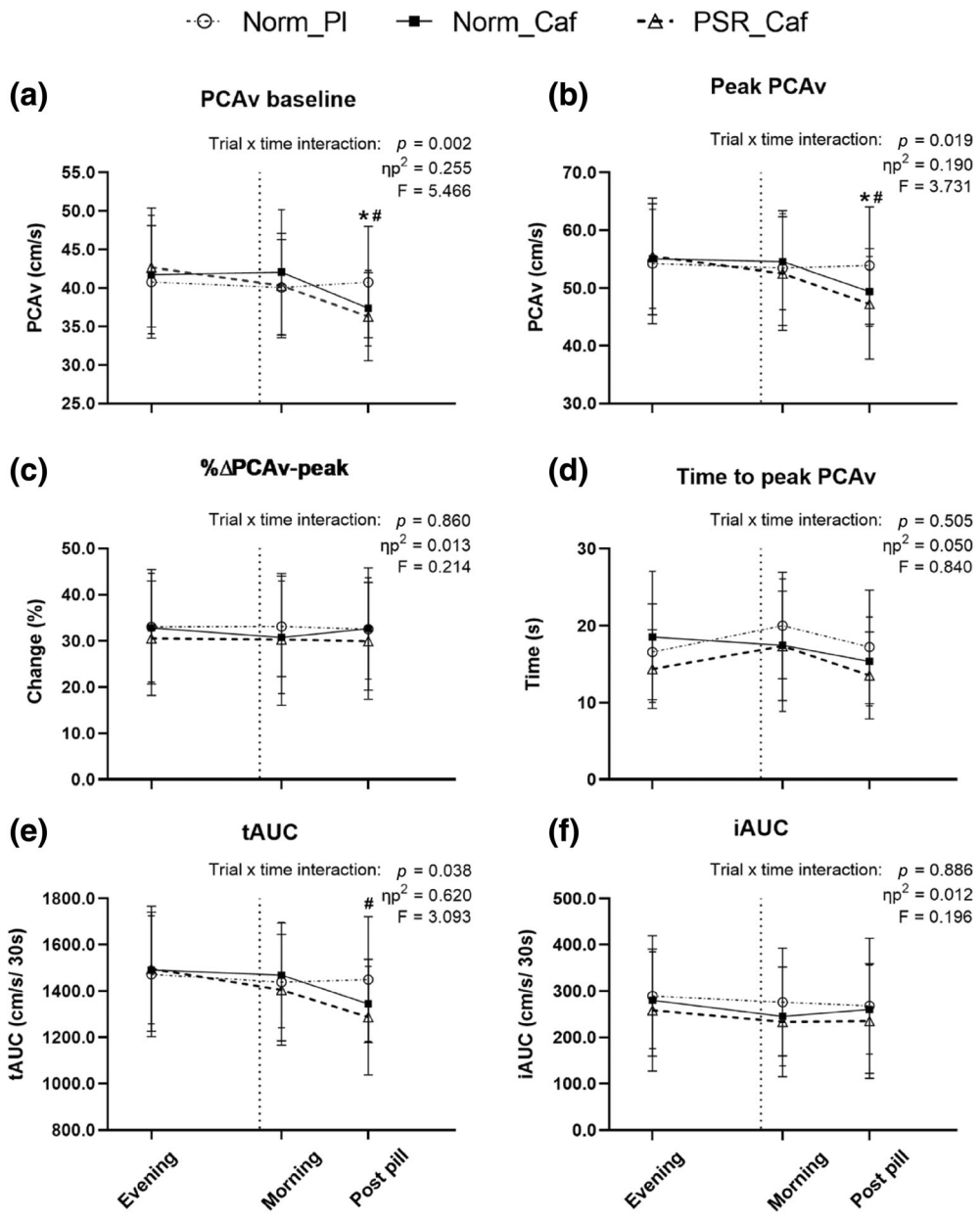

FIGURE 2 The PCAv outcomes during the evening measure, upon arrival at the laboratory after experimental sleep (morning), and 1 h after placebo or caffeine pill ingestion (post pill) (17 participants, nine female). The dotted line indicates the time of waking, i.e., <1 h before the morning visit. Mean and standard deviation are presented, along with the analysis of variance Trial × Time interaction. For all measures degrees of freedom = 4. iAUC, incremental area under the curve; Norm_Caf, normal sleep plus caffeine condition; Norm_Pl, normal sleep plus placebo condition; PCAv, blood velocity through the posterior cerebral artery; PSR_Caf, partial sleep restriction plus caffeine condition; tAUC, total area under the curve. *Significant difference between Norm_Caf and Norm_Pl. #Significant different between PSR_Caf and Norm_Pl.

after placebo (MD +11.2 cm/s/30 s, 95% CI −39.7 to 62.0; $p = 0.648$, $d = 0.04$) (Figure 2e).

At 1 h after pill ingestion, the tAUC was lower in PSR_Caf as compared to Norm_Pl (MD −162.4 cm/s/30 s, 95% CI −260.4 to −64.5; $p = 0.003$, $d = 0.62$), but this was not different between Norm_Caf and Norm_Pl (MD −105.2 cm/s/30 s, 95% CI −212.8 to 2.4; $p = 0.055$, $d = 0.47$).

There was no trial by time interaction effect for %ΔPCAv-peak, time to peak, or iAUC (Figure 2c,d,f).

3.2.2 | The MCAv during cognitive function tests

Data are presented for 14 participants, due to an unattainable MCAv signal at one timepoint for one participant, and cognitive function software issues for two participants, where no alternative testing platform was used. In the PSR_Caf condition, the MCAv baseline was decreased at both the first measurement in the morning (MD −4.6 cm/s, 95% CI −8.3 to −0.8; $p = 0.02$, $d = 0.55$) and after caffeine ingestion (MD −8.8 cm/s, 95% CI 5.9 to −11.7 to −5.9; $p < 0.001$, $d = 1.23$) as compared to the evening measure. The decrease from before to after caffeine did not reach significance (MD −4.2 cm/s, 95% CI −9.1 to −0.6; $p = 0.083$, $d = 0.47$). Morning MCAv was also decreased after caffeine in Norm_Caf (MD −6.1 cm/s, 95% CI −9.5 to −2.6; $p = 0.002$, $d = 0.60$). The MCAv baseline was not different in the Norm_Pl condition from evening to morning before pill ingestion (MD −2.6 cm/s, 95% CI −5.8 to 0.7; $p = 0.110$, $d = 0.29$), or from morning before to after pill ingestion (MD 1.6 cm/s, 95% CI −1.1 to 4.2; $p = 0.217$, $d = 0.15$).

At 1 h after pill ingestion the MCAv baseline was significantly lower in Norm_Caf (MD −6.8 cm/s, 95% CI 1.9 to 11.7; $p = 0.011$,

TABLE 3 Baseline and percentage change in the velocity through the middle cerebral artery during cognitive function tests.

		Norm_Pl, mean (SD)	Norm_Caf, mean (SD)	PSR_Caf, mean (SD)	Trial × Time *p* (η_p^2) *F* value
Baseline MCAv, cm/s					
	Evening	67.0 (9.1)	69.8 (11.5)	69.3 (6.2)	*0.002* (0.281) 5.069
	Morning	69.6 (8.5)	67.3 (10.4)	64.7 (10.0)[#]	
	After pill ingestion	68.0 (11.7)	61.2 (10.4)[*]	60.5 (8.0)[#]	
During cognitive tests %ΔMCAv					
SL, listening	Evening	3.9 (5.1)	0.5 (5.5)	3.5 (5.0)	*0.344* (0.079) 1.112
	Morning	3.1 (5.5)	3.0 (4.9)	5.7 (7.6)	
SL, recall	Evening	5.6 (7.5)	0.3 (6.8)	4.0 (5.5)	*0.271* (0.096) 1.373
	Morning	2.1 (7.2)	1.2 (6.0)	3.7 (5.5)	
N-back	Evening	7.9 (7.8)	4.8 (5.8)	3.9 (4.6)	*0.480* (0.064) 0.884
	Morning	7.6 (5.3)	8.6 (7.5)	7.0 (7.4)	
	After pill ingestion	4.7 (6.1)	3.1 (5.1)	4.1 (5.5)	
Stroop	Evening	4.6 (6.6)	5.9 (9.3)	7.1 (6.0)	*0.053* (0.174) 2.523
	Morning	9.4 (10.1)	5.9 (8.0)	5.4 (8.5)	
	After pill ingestion	4.7 (5.1)	2.9 (6.9)	6.6 (8.6)	
Go/no-go	Evening	7.0 (8.3)	5.0 (7.8)	6.5 (7.0)	*0.580* (0.049) 0.624
	Morning	7.9 (10.7)	5.7 (9.4)	5.0 (8.6)	
	After pill ingestion	7.3 (7.7)	5.7 (6.0)	2.8 (4.9)	

Note: Data are presented as mean (± standard deviation [SD]). Total number of participants 14 (eight females).
Abbreviations: MCAv, blood velocity through the middle cerebral artery; Norm_Pl, normal sleep plus placebo condition; Norm_Caf, normal sleep plus caffeine condition; PSR_Caf, partial sleep restriction plus caffeine condition; SL, shopping list test. Δ% refers to the percentage change from baseline MCAv to average MCAv during the cognitive function test.
[*]Significant difference between Norm_Caf and Norm_Pl.
[#]Significantly different between PSR_Caf and Norm_Pl. For all measures degrees of freedom = 4.

$d = 0.63$) and PSR_Caf (MD −7.5 cm/s, 95% CI 2.8 to 12.2; $p = 0.004$, $d = 0.75$) compared to Norm_Pl.

There were no significant trial by time interaction effects for %Δ MCAv during the cognitive function tests ($p \geq 0.053$, $\eta_p^2 \leq 0.174$) (Table 3).

3.3 | Cognitive function

Cognitive function scores, for any test, showed no difference between conditions or timepoints (time by trial interaction effect $p \geq 0.373$, $\eta_p^2 \leq 0.083$ for all).

4 | DISCUSSION

This study investigated the effects of partial sleep restriction and subsequent caffeine ingestion on NVC in healthy adults. Our primary finding was that NVC was unchanged in the morning after 50% sleep loss. We also observed that morning caffeine consumption consistently reduced baseline cerebral blood velocity, regardless of how a participant slept. However, the relative ability to increase PCAv and MCAv in response to a visual or cognitive challenge respectively, was unaltered by caffeine. Taken together, it appears that NVC remains intact after a 1 night of partial sleep restriction and is unchanged by morning caffeine consumption.

Our finding that NVC was unaltered after sleep restriction is in contrast to the only other experimental data in this field. Csipo et al. (2021) found that 1 night of total sleep deprivation attenuated the NVC response in multiple cortical areas measured with functional near infrared spectroscopy (fNIRS) during a finger tapping task in young healthy adults. Of note, Csipo et al. (2021) utilised total sleep deprivation whilst our study involved 50% sleep restriction, with sleep occurring in the second half of the night. Whether a threshold effect exists between sleep duration and NVC remains to be studied. However, differences between NVC methodologies also cloud our comparisons. fNIRS can determine changes in oxygenation patterns across the cerebral cortex, as opposed to TCD, which provided insight regarding

changes in PCAv and MCAv in the present study. Csipo et al. (2021) also did not observe changes in baseline resting MCAv after sleep deprivation but reported a 4 cm/s decrease in absolute MCAv during n-back cognitive stimulation. Again, this disparate finding could be due to the greater extent of sleep deprivation used in the former study.

The unaltered NVC following sleep restriction in the present study is also contrary to the blunted cerebrovascular function, specifically baseline cerebral blood velocity, cerebral autoregulation, and cerebrovascular reactivity to hypoxia and hypercapnia, observed in patients with OSA (Durgan & Bryan Jr, 2012, Fischer et al., 1987; Urbano et al., 2008). However, the NVC response is likely to be mechanistically different to other measures of cerebrovascular function, given that it targets metabolism rather than the regulatory roles of CO_2 or blood pressure.

The present study also found that the magnitude of the NVC response remained unchanged 1 h after caffeine ingestion, compared to placebo, irrespective of prior sleep. However, baseline MCAv and PCAv, and peak PCAv during the visual search task were ~8–13% lower after caffeine as compared to placebo in both rested and sleep restricted states. This reduction is in line with prior caffeine and cerebral blood flow research in the rested state (Addicott et al., 2009; Chen & Parrish, 2009; Field et al., 2003; Vidyasagar et al., 2013; Xu et al., 2015). As caffeine decreases baseline cerebral blood flow, the oxygen extraction fraction is expected to increase in order to meet the metabolic demands of the brain (Chen & Parrish, 2009). Indeed, Xu et al. (2015) found ingestion of 200 mg of caffeine resulted in decreased cerebral blood flow, no change in cerebral metabolic rate but an increased oxygen extraction fraction. Additionally, fNIRS data are available that indicate alterations in prefrontal oxygenation during cognitive challenges after partial sleep restriction (Pan et al., 2019). It is therefore plausible that in the present study, whilst both absolute MCAv and PCAv after caffeine ingestion were not significantly different between the rested and the sleep-restricted state, the oxygen extraction fraction may have differed.

Acute sleep restriction is also associated with impaired cognitive function (Lowe et al., 2017). However, the present study did not find any sleep restriction induced changes in cognitive function. This is in line with the findings of Schaedler et al. (2018) who evaluated the effects of partial morning, partial evening, and normal sleep on executive functioning in healthy young adults. Whilst other studies utilising a longer sleep deprivation protocol have reported cognitive deficits (Cain et al., 2011; Chuah et al., 2006; Drummond et al., 2006), studies with similar sleep restriction protocol typically report that cognitive function is unchanged (Rossa et al., 2014; Schaedler et al., 2018). It therefore appears that, alongside NVC, cognitive function is resilient to 1 night of partial sleep restriction in this population.

This study provides novel insight into the effects of partial sleep restriction and subsequent caffeine ingestion on NVC. The implementation of an ecologically valid sleep-restriction protocol that may reflect intentional sleep loss due to socialising, work demands, caring duties etc., or an unplanned poor night of sleep, is a strength of the present study. Furthermore, the amount of deep sleep accrued in 1 night decreases with age (Li et al., 2018) and is further decreased in patients with Alzheimer's disease (Avidan, 2006). Therefore, to mimic the changes in sleep architecture that occur with ageing and disease, this study required participants to stay awake during the first half of the night in an attempt to deprive them specifically of deep, slow-wave sleep (Dijk, 2009; Léger et al., 2018). Based on Actiheart device recordings, the intervention more than halved participants' total deep sleep, although future studies should consider utilisation of polysomnography, the 'gold standard' method of sleep staging.

Despite the novelty of our study, we acknowledge that we are unable to extrapolate our findings beyond a single night of sleep loss in healthy adults. It remains to be seen if NVC is similarly intact after similar sleep loss in older adults, or in those with cerebrovascular disease risk factors, or habitual 'poor sleepers'. The acute vascular response to a challenge can also be influenced by behavioural cardiovascular risk factors (Karatzi et al., 2007). Whether NVC is acutely altered after a single night of partial sleep loss in those who have disrupted sleep or sleep patterns (i.e., shift workers), remains an interesting research question. The health of the participants in the present study was not verified by physical examination, nor was their sleep assessed using polysomnography, thus we cannot guarantee the absence of any underlying, undiagnosed, sleep or health conditions that may interact with our main outcomes.

It is also important to consider the present work in light of a number of other methodological considerations. Firstly, habitual caffeine consumption was relatively heterogenous within our sample, and the abstinence period was only ~24 h. Given that withdrawal in habitual caffeine users can alter cerebral blood flow differentially to non-habitual users, this limitation may explain some of the inter-individual differences in vascular responses (Field et al., 2003). In addition to this, NVC was measured using TCD. As the diameter of the insonated vessel is unknown, TCD measures cerebral blood velocity, not absolute volumetric flow, and in turn can only be used as a surrogate of cerebral blood flow if the diameter of the insonated vessel remains constant (Willie et al., 2011). Furthermore, although cerebral circulation is known to be at least partly regulated by the partial pressure of arterial CO_2 ($PaCO_2$), we did not measure expired gases as an indicator of $PaCO_2$ in the present study. However, previous NVC studies using TCD have shown expired end tidal CO_2 remains within ±5 mmHg of eucapnia during such tasks (Smirl et al., 2016; Zaletel et al., 2004). Therefore, minimal changes in PCA diameter are anticipated. A further limitation of our NVC measurement tool is the sole focus on cerebral blood velocity without a measure of metabolism or oxygen extraction fraction. Future NVC and sleep-restriction studies should consider the addition of NIRS to complement the TCD data in this manner, or if available, calibrated blood oxygenation level dependent measures.

In conclusion, this study provides insight into the effects of partial sleep restriction and subsequent caffeine ingestion on NVC. We found that NVC was unaltered after 50% sleep loss, and caffeine did not modify the magnitude of the NVC response in either the rested or the sleep-deprived state. These novel findings highlight the necessity for further research into the relationship between sleep and the

cerebrovasculature, specifically whether habitual sleep quantity and quality affects different measures of cerebrovascular function.

AUTHOR CONTRIBUTIONS

Alice Lester B: Conceptualization; investigation; writing – original draft; methodology; writing – review and editing; formal analysis. **Gavin Buckingham:** Conceptualization; writing – review and editing; supervision. **Bert Bond:** Conceptualization; investigation; writing – review and editing; supervision; methodology.

ACKNOWLEDGEMENTS

The authors would like to thank all participants for their time and dedication to this study.

FUNDING INFORMATION

This study was not supported by external funding.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest, financial or otherwise, are declared by the authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Lester, A. B., Buckingham, G., & Bond, B. (2024). The effects of partial sleep restriction and subsequent caffeine ingestion on neurovascular coupling. *Journal of Sleep Research*, e14145. https://doi.org/10.1111/jsr.14145