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ORIGINAL ARTICLE

# The wake maintenance zone shows task dependent changes in cognitive function following one night without sleep

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## Abstract

**Study Objectives:** The interaction between homeostatic sleep pressure and circadian timing modulates the impact of sleep deprivation on cognition. We aimed to investigate how this interaction affects different cognitive functions.

**Methods:** Twenty-three healthy volunteers (18 males; mean age = 25.4 ± 5.7 years) underwent 40 hours of sleep deprivation under constant routine conditions. Performance on the Psychomotor Vigilance Test and a cognitive battery assessing vigilant attention, complex attention, recognition memory, and working memory was assessed in the morning (27 hours awake) and evening (37 hours awake) during sleep deprivation and compared to well-rested performance 24 hours earlier. Circadian phase assessments confirmed evening tests occurred in the wake maintenance zone (WMZ).

**Results:** Increased time awake significantly impacted performance on all measures except recognition memory. Post hoc analyses found performance on all measures was significantly impaired in the morning following 27 hours of sleep deprivation compared to well-rested performance 24 hours earlier. In contrast, complex attention and working memory were preserved in the WMZ after 37 hours awake compared to 24 hours earlier, while vigilant attention and PVT performance were significantly impaired. During sleep deprivation, composite scores of speed and accuracy were both impaired in the morning, while only speed was impaired during the WMZ.

**Conclusions:** We observed task- and time-dependent effects of sleep deprivation, such that vigilant attention was significantly impaired after both 27 hours and 37 hours awake (compared to when well-rested at the same circadian clock time). In contrast, complex attention and working memory were impaired at 27 hours awake, but preserved in the WMZ despite increased homeostatic sleep pressure (37 hours awake).

### Statement of Significance

Sleep deprivation adversely affects cognitive performance, though its impact is modulated by circadian timing. While previous studies describe how the circadian system adversely impacts performance in a task-dependent manner during sleep loss (i.e. during the night-time hours), we provide evidence that the circadian system also preserves performance in a task-dependent manner during sleep loss (i.e. during the wake maintenance zone [WMZ]). While vigilant attention was impaired during sleep deprivation regardless of circadian timing, working memory and complex attention were impaired following 27 hours awake, yet preserved in the WMZ following 37 hours awake. Workplaces where employees routinely experience inadequate sleep may be able to improve safety and productivity by scheduling accuracy-sensitive work at more optimal circadian times.

**Key Words:** sleep deprivation; cognitive function; circadian rhythms; melatonin; DLMO; wake maintenance zone

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## Introduction

Insufficient sleep has an adverse impact on health and a wide range of cognitive functions [1]. While sleep deprivation can result in greater performance deficits on measures of particular cognitive domains, especially those assessing simple reaction time (RT) [2], it is not fully understood how these task-specific vulnerabilities may be differentially affected by a combination of circadian and homeostatic factors.

Both increased time awake and circadian timing impact cognitive performance. When wake is extended beyond the normal 16-hour day, cognitive performance deteriorates [3–5]. Circadian timing can modulate performance outcomes both favorably and unfavorably. For instance, performance can be impaired at adverse circadian times even in well-rested participants [6–8], or improved at favorable circadian times [6, 8], even in sleep-deprived participants [9]. The wake maintenance zone (WMZ) is a 2- to 3-hour phase prior to the evening onset of melatonin secretion where the circadian system maximally promotes wakefulness [10, 11] and performance [6, 12]. While a recent study reported evidence of task-dependent effects when the circadian system is adversely affecting performance (i.e. during times of circadian misalignment during a simulated night shift study) [13], no study has examined task-dependent effects when the circadian system is promoting performance, that is, during the WMZ.

During sleep deprivation, the magnitude of impairment is generally greater on tasks measuring simpler aspects of cognition, compared to tasks that require complex or integrative cognitive operation. In a meta-analysis of 70 studies, where tests were grouped into six broad cognitive domains, and outcomes reported as either accuracy, RT, or attentional lapses [2], performance on simple attention tasks like the Psychomotor Vigilance Test (PVT) showed the greatest vulnerability to sleep deprivation, with large effect sizes for lapses and RT. Performance on more complex tasks was comparatively less vulnerable to 24–48 hours sleep deprivation. The extent to which this task-dependent effect of sleep deprivation is observed during the WMZ, where performance is optimal, is unknown. Moreover, it is of particular importance given that cognitive function following one night of sleep deprivation is commonly tested in either the early morning (~22–26 hours post-wake) or evening (~34–37 hours post-wake), corresponding to the circadian nadir and peak in performance, respectively. In addition, some studies compare sleep deprivation to well-rested conditions at the same circadian or clock time [14, 15], while others do not [16–18]. In tests scheduled 22–26 hours post-wake, processing speed [19], working memory [20, 21], and complex attention, such as tests of response inhibition [22], are adversely impacted by one night of sleep deprivation. In tests scheduled 34–37 hours post-wake, verbal memory [23, 24], working memory [25], social decision-making [26], and complex attention [27–29] are impaired. In protocols where the same test was completed in the morning and evening, some have reported no differences between morning and evening on working memory [25] and response inhibition [18], while one group found improved performance on tests of working memory and visual discrimination at 38 hours of wakefulness relative to 25 hours [30]. Understanding whether these differences are due to task-dependent effects observed in the WMZ, or due to differences in study design, timing of test administration, and test characteristics is challenging.

We sought to address this challenge by assessing the impact of sleep deprivation on multiple tasks in both the morning and evening, compared to when well-rested at the same circadian time (i.e. 24 hours earlier). For evening tests, we will ensure task administration is within the WMZ. In addition, to minimize confounding aspects of task characteristics, we employed a cognitive battery of four tests of attention (simple and complex) and memory (recognition and working) with comparable duration and near-identical visual presentation.

## Methods

### Participants

Twenty-three healthy young adults (18 men, 5 women), aged 25.43 ± 5.67 (*M* ± *SD*) years, participated. Ethical approval for all procedures was obtained from the Monash University Human Research Ethics Committee (CF14/2790 – 2014001546). Participants gave written informed consent. Participant eligibility criteria included: fluency in English, no shift work (5 or more hours worked between 10:00 pm and 07:00 am) within the last 3 months, no transmeridian travel across three or more time zones in the past month, a body mass index between 18.0 and 29.9 kg/m$^2$, no history of medical, psychiatric or sleep disorders, and no reported use of illicit drugs within the last year, or consumption of caffeine exceeding 300 mg/day or alcohol exceeding 14 standard units/week. Women were not currently pregnant or using hormonal contraception, and were studied in the laboratory during the follicular phase of their menstrual cycle. All participants were deemed medically and psychologically healthy following a full medical history and examination by a physician, including electrocardiogram and blood and urine tests, and an interview with a clinical psychologist. They refrained from consuming alcohol and caffeine, or using nicotine, supplements, or prescription or non-prescription drugs in the 3 weeks prior to admission to and throughout the laboratory study. Compliance was verified by a urine toxicology screen and breathalyzer assessment on their arrival for the laboratory assessment. All reported habitual bedtimes between 09:30 pm and 01:00 am, habitual wake times between 05:30 am and 09:00 am, and sleep duration between 7 and 9 hours with no more than one nap per week. A flowchart of participant recruitment can be found in the Supplementary Material (S1).

### Pre-laboratory protocol

For 3 weeks prior to the laboratory assessment, each participant wore an Actiwatch Spectrum (Philips Respironics, BMedical, QLD, Australia), completed a daily sleep diary, and made a time-stamped call-in message when they woke and when they went to bed. For the first week, participants were free to select their bed and wake times. For the 2 weeks immediately prior to the laboratory assessment, they adhered to a strict 8:16 hours sleep:wake schedule, with a consistent bed and wake time. Compliance with this schedule was verified by actigraphy and their call-ins.

### Laboratory protocol

#### *General conditions*

Participants were studied in a private, sound-attenuated suite free of time cues for 6 days. Ambient light levels were strictly controlled (see below). Temperature was maintained at 21°C ± 2°C. A full polysomnographic assessment was completed during

the first sleep episode. Participants were excluded if a sleep disorder was identified.

The laboratory protocol (Figure 1) included 2 baseline days, 40 hours of continuous wakefulness under constant routine (CR) conditions and 2 recovery days. During the baseline days, participants maintained their structured 8:16 hours sleep:wake schedule from their last 2 weeks of at-home monitoring. Recovery sleep opportunities were extended to 12 hours, though participants were permitted to get up earlier if they were unable to sleep. Light levels were strictly controlled throughout the study: mean maximum ambient light during baseline and recovery wake episodes was ~102 ± 37 lux (horizontal plane) and ~45 ± 21 lux (vertical plane), and ~3 ± 1 lux (horizontal) and ~1 ± 3 lux (vertical) during CR and the last 5 hours of the second baseline day. Lights were turned off during sleep episodes. Ambient lighting illuminance was measured on each day of the protocol at four locations directly under light panels in the suite at a height of approximately 1.8 m using a light meter (Tektronix J17 Luma Color, Oregon). Lighting was generated from ceiling-mounted Philips 4100K fluorescent bulbs (Master TL5 HE 28W/840 cool lights, Philips Lighting, Amsterdam, Netherlands), covered with neutral density filters (3-stop LEE Filters, Lightmoves, Noble Park, Australia), which provided broad-spectrum white light with a peak of 545 nm and correlated color temperature (CCT) of 3968K (UPRTek MK350N Spectrometer, Taiwan). During wake periods other than the CR, participants were free to move around the suite and engage in quiet activities when not completing tests.

### *Constant routine*

Participants woke to CR conditions after their second baseline night. The CR protocol is designed to minimize or remove environmental time cues that influence the rhythms of the participant's body clock [31]. Throughout the 40 hour CR, participants remained in bed in a semi-recumbent posture, and were not permitted to make any significant postural changes. They consumed hourly isocaloric snacks (a quarter sandwich, with 60 mL of water and 40 mL of apple juice), with a macronutrient content in line with the Australian Dietary Guidelines 2013 [32]. Urine voids and bowel movements were completed in bed with either a metal urinal or bedpan. To ensure they remained awake, participants were continuously monitored by a staff member in the suite, except during urine voids and bowel movements. A computer was wheeled over the bed for participants to complete tests during the CR; this was designed to allow participants to comfortably view the screen and complete the tests while maintaining constant posture.

### *Cognitive testing*

Participants completed one practice of each test on the first baseline day. Previous research has shown that performance on the Cogstate Brief Battery (CBB) stabilizes after one practice session (Cogstate, Melbourne, Australia) [33–35].

Participants completed the CBB four times during the CR, shown by the inverted triangle in Figure 1. Two administrations were in the morning, 24 hours apart, at 3 hours and 27 hours post habitual wake, and two were in the evening, also 24 hours apart, at 13 hours and 37 hours post habitual wake (equivalent to 11:00 am and 09:00 pm for a participant with an 08:00 am waketime). The CBB comprises four computerized tests that take approximately 10–12 minutes in total to administer. The tests are presented in the same sequence, with near-identical visual presentation, and have standard instructions that appear on the screen for the experimenter to read to the participant. In each test, participants are instructed to attend to a facedown playing card in the center of the screen, and respond to a question specific to the task when the card flips over. Participants were asked to respond as quickly and accurately as possible in all tests by clicking the left mouse button for "Yes" or the right mouse button for "No" with the hand they usually use to operate

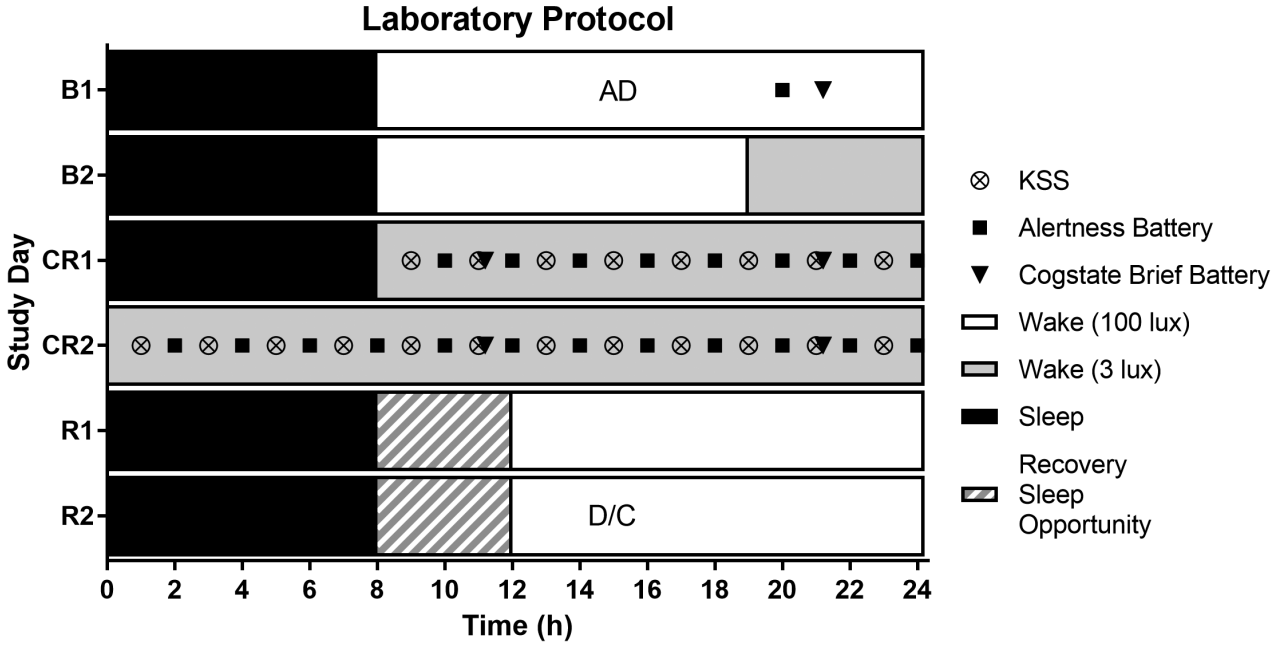


**Figure 1.** Raster plot of the laboratory protocol (nominal 08:00 am waketime). B, baseline; R, recovery; AD, admission; D/C, discharge. Symbols indicate the timing of tests: Crossed circles represent the KSS; black squares represent the Alertness Battery comprising the KSS and the Psychomotor Vigilance Task (PVT); black inverted triangles represent the CBB.

a mouse. The CBB has been validated as a measure of cognitive impairment in neurodegenerative conditions [33, 36], pharmacologically-induced sedation [37, 38], and sleep deprivation [39].

The four tests comprising the CBB largely assess the domains of attention and memory [40–42].The tasks are as follows:

***Attention.*** Detection (DET) task—a simple RT test. Participants are asked "Has the card turned over?" and must press the "Yes" button as quickly as possible when it does. The task continues until either 25 correct responses are recorded, or the maximum time of 2 minutes is reached.

Identification (IDN) task—a choice RT test. Participants are asked "Is the card red?" and must press the "Yes" button if it is, and the "No" button if it is not. The task continues until 35 correct responses are made, or until the maximum time of 2 minutes is reached.

For both DET and IDN, anticipatory responses (those made before the card flips over) and timeouts (responses longer than 3.5 s) are considered incorrect trials and removed from the analysis. The primary outcome of each task is RT in milliseconds. These tasks measure different aspects of attention. DET, as a simple RT task, presents a single stimulus to which participants are required to make a single response: this measures vigilant attention [41, 43]. IDN, as a two-choice RT task, requires participants to first identify which of two stimuli has been presented, then select and make the correct response from two alternatives. This reflects both information processing speed and more complex attention [2, 41, 43].

***Memory.*** One Card Learning (OCL) task—Participants are asked "Have you seen this card before in this task?"; when the card flips over, they must press the "Yes" button if the card has been presented previously, and the "No" button if not. Six randomly selected cards will repeat throughout the task; the others are used as non-repeating distractors interspersed between them. The task continues until either 42 correct responses are made, or the maximum time of 3 minutes is reached.

*One Back (ONB) task*—Participants are asked "Is this card the same as that on the immediately previous trial?". When the card flips over, participants must press the "Yes" button if it is the same as the card presented immediately before it, and the "No" button if it is not. The task continues until either 42 trials have been responded to (correctly or incorrectly), or until the maximum time of 3 minutes is reached.

The primary outcome of both OCL and ONB is the percentage of correct responses (accuracy), expressed as a decimal with a maximum value of 1.0 (e.g. 90% correct responses would be expressed as an accuracy of 0.9). These tasks assess different aspects of memory. As an *n*-back task, ONB assesses working memory [21, 41], while OCL assesses recognition memory [33, 34].

***KSS and PVT.*** From 2 hours after waking to CR, participants completed a bi-hourly computerized test battery containing the Karolinska Sleepiness Scale (KSS) and a visual PVT. The KSS was also administered by itself on the alternate hour. The KSS is a one-item questionnaire that asks participants to indicate on a scale of 1–9 how sleepy they have been feeling over the previous 5 minutes [44]. The modified version with descriptors identified on each point was utilized [45]. The PVT required participants to monitor a white rectangle centered on the screen, and press a button on a handheld response box with their dominant thumb as quickly as possible each time a stopwatch stimulus appeared and began counting up from zero. Once the participant responded, the stopwatch briefly displayed their RT in milliseconds before resetting. The stimulus appeared at random intervals between 2 and 10 seconds after the previous response. If the participant made no response within 5000 ms, an alerting tone played. Any response <100 ms was removed from the data during cleaning, including anticipatory responses. Mean response time and number of lapses were calculated.

### *Melatonin measurement*

Blood samples were taken each hour via an in-dwelling intravenous cannula to assess participants' plasma melatonin levels, a marker of circadian timing [46]. The cannula was inserted into either a forearm or antecubital vein approximately 1 hour after waking to CR. Samples were centrifuged at 2700 rpm for 10 minutes at 4°C to separate the plasma layer, either immediately or after temporary refrigeration at 4°C. A 1 mL aliquot was taken from each sample, snap frozen in dry ice, and stored at –20°C until assayed. Total blood plasma melatonin concentration was determined at the Adelaide Research Assay Facility by reverse-phase C-18 column extraction of 500 µL plasma, followed by double antibody radioimmunoassay using standards and reagents supplied by Buhlmann Laboratories (RKMEL-2, Buhlmann Laboratories AG, Schönenbuch, Switzerland). This assay is based on the Kennaway G280 anti-melatonin antibody [47, 48] and [125I]2-iodomelatonin as the radioligand and follows the protocol provided by Buhlmann. The limit of detection of the assay using 500 µL of extracted plasma was 1.0 pg/mL. Samples were sent in four batches. All samples from an individual were measured in a single assay. Samples were assayed in duplicate and the range of the intra-assay coefficients of variation was 5.5–9%. The range of the inter-assay coefficients of variation of the low concentration quality control was 5.3–13.3%; the range of the inter-assay coefficients of variation of the high concentration quality control was 7.3–17.7%.

## Data analysis

Data were collected from 23 participants. KSS data includes all 23 participants. CBB data was collected from $n = 21$ participants ($n = 1$ lost due to failed data quality checks; $n = 1$ removed due to not completing all four test sessions). Following dim light melatonin onset (DLMO) assessment, evening task administration for $n = 3$ did not fall within the WMZ. These were removed from the CBB analyses, leaving a total of $n = 18$. PVT data are described for 14 participants only (of the 23 participants, $n = 9$ were lost due to technical difficulties with the task).

### *DLMO calculation*

DLMO times were calculated for each participant as the time at which the concentration of plasma melatonin first exceeded 5 pg/mL, based on the melatonin conversion factor of 4.304778 [49], using linear interpolation between the samples immediately prior to and after the threshold. Where possible, DLMO time was calculated from the first evening rise in melatonin levels observed during CR, and assigned a circadian phase of 0. Where DLMO was not accurately identified at this point ($n = 4$, due to missing samples), it was calculated during the second melatonin cycle near the end of the CR. In the 11 participants for whom it was possible to calculate both DLMO times, the times did not significantly differ, $t(10) = 0.63$, $p = .54$,

and were highly correlated, $r = 0.94$. Tests were deemed to have occurred in the WMZ if they were begun in the 3-hour period prior to DLMO [9], including those calculated to have begun within 5 minutes of DLMO (Figure 2). Results on the CBB were only reported for those participants who completed the evening batteries within the WMZ.

### *Transformations*

To normalize the distributions of the Cogstate data, a logarithmic base 10 transformation was applied to RT outcomes, and an arcsine square-root transformation was applied to the accuracy outcomes [42]. All PVT RTs were normalized with a reciprocal ((1/RT) * 1000) transformation. Lapses were transformed with a square-root transformation [(*n*) + (*n*+1)] to normalize the distribution [50].

### *Calculation of Cogstate composite scores*

To express the magnitude of cognitive decline during sleep deprivation across tasks, and on a comparable scale, we calculated standardized RT and accuracy composite change scores for the Cogstate battery based on previously reported methodologies [38, 51]. This was calculated for morning (3 hours vs. 27 hours) and evening (13 hours and 37 hours) tests separately using the following equation:

$$\frac{\text{Sleep Deprived Score} - \text{Well Rested Score}}{\text{within-subjects } SD}$$

Change scores for RT tests were reversed such that a negative change score indicates decline from baseline on all tests. Change scores were standardized using a within-subjects *SD* [52] drawn from age-based normative data for the tests (Supplementary Table 1). An accuracy composite change score was calculated by averaging the standardized change scores on OCL and ONB, and a RT composite change score was calculated by averaging standardized change scores on DET and IDN. The accuracy composite thus reflects performance on memory tasks, while the RT composite reflects performance on attention tasks [42].

### *Analyses*

The effect of sleep deprivation on each performance measure was analyzed using a linear mixed model, as this approach accommodates missing data and inter-individual variability. Time awake was modeled as a fixed effect, and participant was modeled as a random effect. A compound symmetry covariance structure was used for all models except for DET and KSS, for which a first-order autoregressive covariance structure was used. For all models, the covariance structure that produced the lowest Schwarz Bayesian Information Criterion (BIC) value was used [53]. Pairwise comparisons were run post hoc to test for differences between well-rested and sleep-deprived performance in the morning and evening. Performance on the CBB tests was compared between 3 hours and 27 hours (morning) and 13 hours and 37 hours (evening). KSS scores, PVT mean RT and number of lapses were taken from the test session prior to each CBB administration: the morning PVT/KSS tests were thus taken at 2 hours and 26 hours post-wake, and the evening tests at 12 hours and 36 hours post-wake. Cogstate composite scores were tested against a mean of zero with one-sample *t*-tests. A false discovery rate (FDR) adjustment was used to control for familywise error [54, 55] for the post hoc tests and the one-sample *t*-tests. Adjusted *p*-values ($p_{adj}$) are presented for all these tests, using the FDR "*q*" adjusted significance value. Cohen's *d* was calculated as an estimate of effect size for all comparisons; effect sizes were classed as small ($0.2 < d < 0.5$), medium ($0.5 < d < 0.8$) or large ($d > 0.8$) according to Cohen's criteria [56]. Cohen's *d* values are reported as negative if performance deteriorated. All statistical analyses were performed using SPSS 21.0 (IBM Corp., Armonk, NY).

## Results

### Cogstate battery results

Table 1 summarizes the descriptive statistics and effect size estimates for all post hoc comparisons. Increased time awake

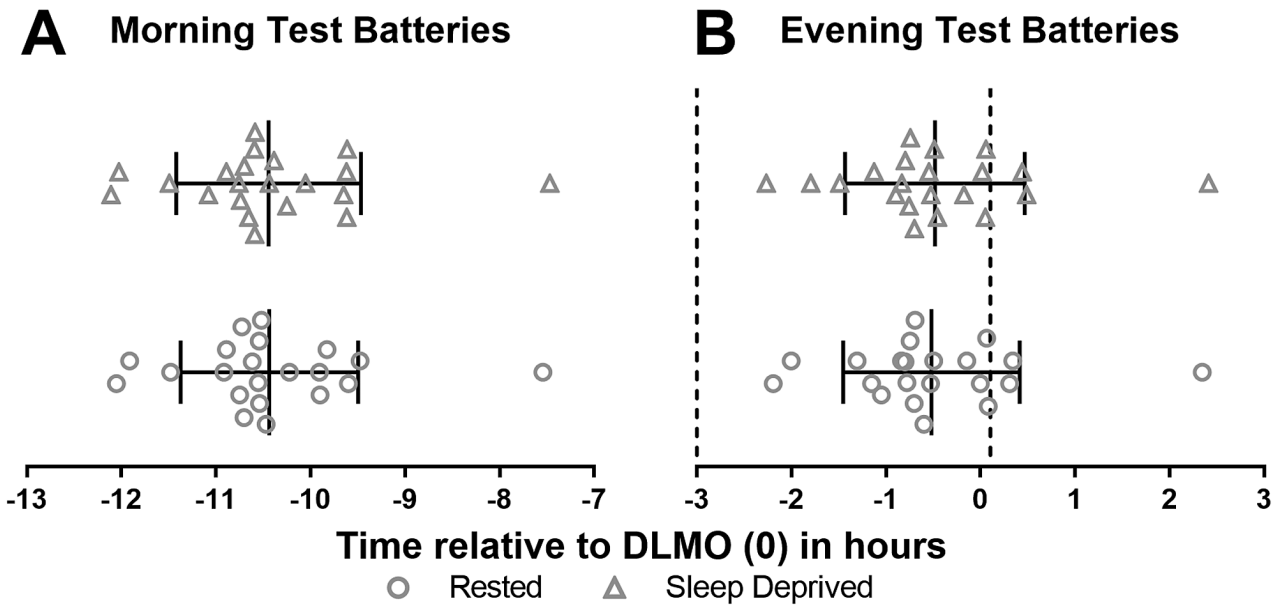


**Figure 2.** Distribution of the circadian timing of each Cogstate battery. (A) Morning tests; (B) evening tests. Black lines with error bars represent the means and *SD*s. Symbols are times individual participants began the battery. The dotted lines enclose tests deemed to have begun in the WMZ: from 3 hours prior to DLMO to 5 minutes after. Mean DLMO time was 21:01 (*SD* 1 hours 12 minutes); the mean phase angle between DLMO and scheduled bedtime was 2 hours 5 minutes (*SD* 56 minutes).

**Table 1.** Descriptive Statistics for Post hoc Comparisons

| Test | Outcome | Unit | Time of day | Rested | | Sleep deprived | | Adjusted p value | Cohen's d |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Mean | SD | Mean | SD | | |
| DET | RT | Log 10 transformed milliseconds | Morning | 2.47 | 0.07 | 2.55 | 0.10 | <.0001 | −0.97 |
| | | | Evening | 2.46 | 0.06 | 2.53 | 0.10 | .0009 | −0.84 |
| IDN | RT | Log 10 transformed milliseconds | Morning | 2.69 | 0.07 | 2.75 | 0.08 | .0017 | −0.69 |
| | | | Evening | 2.70 | 0.07 | 2.72 | 0.07 | .1277 | −0.34 |
| OCL | Accuracy | Arcsine percentage accuracy | Morning | 1.08 | 0.11 | 1.01 | 0.15 | -* | −0.57 |
| | | | Evening | 1.06 | 0.10 | 1.04 | 0.12 | -* | −0.20 |
| ONB | Accuracy | Arcsine percentage accuracy | Morning | 1.45 | 0.11 | 1.29 | 0.16 | .0072 | −1.16 |
| | | | Evening | 1.39 | 0.15 | 1.40 | 0.16 | .7420 | 0.03 |
| PVT | RT | Reciprocally transformed milliseconds | Morning | 3.38 | 0.36 | 2.42 | 2.42 | <.0001 | −1.77 |
| | | | Evening | 3.42 | 0.34 | 2.73 | 2.73 | <.0001 | −1.81 |
| | Lapses | Square-root transformed lapses | Morning | 2.59 | 1.74 | 9.36 | 3.21 | <.0001 | −2.37 |
| | | | Evening | 2.49 | 1.45 | 6.81 | 3.20 | <.0001 | −1.69 |
| KSS | Sleepiness | KSS Score | Morning | 3.74 | 0.92 | 6.74 | 1.68 | <.0001 | −2.57 |
| | | | Evening | 3.96 | 1.19 | 5.68 | 2.12 | .0001 | −1.22 |

This table summarizes the means, SDs, adjusted *p*-values, and Cohen's *d* calculated from the means and pooled SDs.
*Post hoc tests were not run on OCL as the main effect of time awake was not significant.

significantly increased mean RT on DET ($F_{3, 50.45} = 9.59$, $p < .0001$). Post hoc tests found that mean RT on DET was significantly longer at 27 hours relative to 3 hours ($p_{adj} < .0001$), and at 37 hours relative to 13 hours ($p_{adj} = .001$); effect sizes were large, $d = -0.97$ and $-0.84$, respectively. Mean RT also increased on IDN with time awake ($F_{3, 53.12} = 6.37$, $p = .001$); however, mean RT on IDN was significantly longer at 27 hours relative to 3 hours ($p_{adj} = .002$), but not at 37 hours compared to 13 hours ($p_{adj} = 0.11$), $d = -0.69$ (a medium effect size) and $-0.34$, respectively. Mean accuracy on ONB showed the same trend: there was a main effect of time awake on performance, ($F_{3, 53.37} = 3.37$, $p = .012$), while post hoc tests showed performance was significantly poorer at 27 hours compared to 3 hours, with a large effect size ($p_{adj} = .007$, $d = -1.16$), but not at 37 hours compared to 13 hours ($p_{adj} = .74$, $d = 0.03$). There was no main effect of time awake on OCL ($F_{3, 53.11} = 2.09$, $p = .11$), though there was a medium size difference between performance at 27 hours compared to 3 hours ($d = -0.57$). While analyses were performed on transformed data (see Data Analysis section), raw data are plotted for ease of interpretation (Figure 3). For the composite change scores, a value of 1 is equivalent to a change in performance of one within-subjects *SD*. The RT composite change score significantly deteriorated at 27 hours, $t(17) = 4.87$, $p_{adj} = .0006$, $d = -1.15$, and 37 hours, $t(17) = 3.74$, $p_{adj} = .003$, $d = -0.88$, while the accuracy composite change score deteriorated at 27 hours, $t(17) = 3.50$, $p_{adj} = .003$, $d = -0.82$, but was unchanged at 37 hours awake, $t(17) = 4.87$, $p_{adj} = .72$, $d = -0.08$ (Figure 4).

### Alertness-vigilance battery results

To validate that the protocol provided the expected circadian- and wake-dependent changes, we analyzed the PVT data from the subset of participants with those data. Subjective and objective indices of alertness change were observed across the protocol, such that alertness was lowest during the biological night and highest during the first 16 hours of the CR (Figure 5). PVT performance significantly declined with time awake (Figure 6): Post hoc tests showed mean RT was significantly greater at 26 hours relative to 2 hours awake, with a large effect size, $p_{adj} < .0001$, $d = -1.77$, and at 36 hours relative to 12 hours, with a large effect size, $p_{adj} < .0001$, $d = -1.81$. Lapses also significantly increased at both 26 hours and 36 hours compared to well-rested performance 24 hours prior (2 hours and 12 hours) with large effect sizes, $p_{adj} < .0001$, $d = -2.37$ and $p_{adj} < .0001$, $d = -1.69$, respectively. KSS scores showed a similar pattern: self-reported sleepiness was significantly higher at 26 hours compared to 2 hours, and 36 hours compared to 12 hours, with large effect sizes: $p_{adj} < .0001$, $d = -2.57$, and $p_{adj} < .0001$, $d = -1.22$, respectively.

## Discussion

Our findings show that the deterioration in cognitive performance during sleep deprivation is both task- and time-dependent. Simple, sustained attention, as measured by the PVT and DET, was significantly poorer following >24 hours of sleep deprivation compared to well-rested performance, regardless of whether testing occurred in the morning, or in the evening during the WMZ. In contrast, complex attention (IDN) and working memory (ONB) were impaired during sleep deprivation when tested in the morning (27 hours awake vs. a circadian matched well-rested baseline at 3 hours awake), but were preserved when tested in the evening during the WMZ (37 hours awake vs. a circadian matched well-rested baseline at 13 hours awake), despite the increased homeostatic sleep pressure at this time. Recognition memory (OCL) did not show an overall effect of sleep deprivation, yet showed evidence of the same pattern of results as complex attention and working memory: performance was poorer at 27 hours relative to 3 hours (a medium effect size of $d = -0.57$) but not at 37 hours relative to 13 hours ($d = -0.20$). Moreover, change in aggregated performance to reflect speed and accuracy across tasks following one night without sleep also differed with the time of testing: both speed and accuracy were impaired during morning testing, while speed slowed and accuracy was preserved during evening testing in the WMZ.

Our findings are consistent with our earlier work investigating the impact of the WMZ on cognitive performance during 50 hours of sleep deprivation [9]. Here, vigilant attention (PVT) and information processing speed (the digit symbol substitution

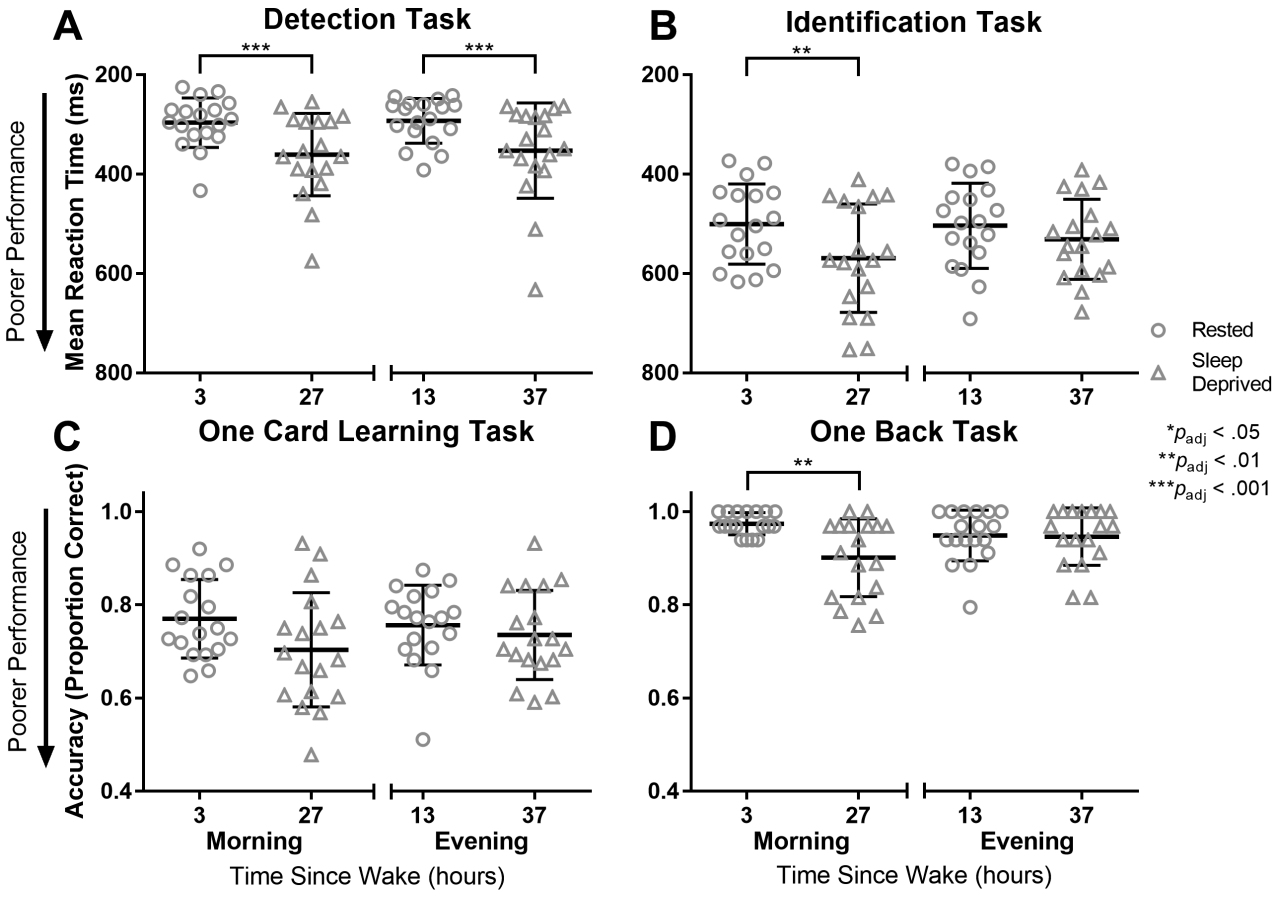


**Figure 3.** Comparison between well-rested and sleep-deprived performance on the CBB at the same time of day. (A) Mean reaction time in milliseconds on Detection; (B) Mean reaction time in milliseconds on Identification; (C) Accuracy (proportion of trials correct, where 1.0 indicates perfect accuracy) on One Card Learning; (D) Accuracy on One Back. Black lines with error bars represent the means and SDs; symbols represent individual performance. Sleep-deprived and well-rested performance was compared in the morning (3 hours vs. 27 hours awake; left of each figure) and in the evening (13 hours vs. 37 hours awake; right of each figure).

task [DSST]) was improved in the WMZ, relative to performance earlier in the same day. We calculated the magnitude of change (Cohen's *d*) between well-rested and sleep-deprived performance in the WMZ in this study, and compared it to our current findings. For vigilant attention, the magnitude of change when sleep deprived and in the WMZ was comparable between studies: PVT raw RT ($d$ = 1.04 for both studies) and lapses ($d$ = 1.43 (current) and $d$ = 2.04 [Shekleton *et al.*]) were both poorer when sleep deprived, with large effect sizes [56]. DSST performance in the WMZ, however, was poorer when sleep deprived in our previous study ($d$ = 0.52, a medium effect size) [57], while performance on IDN, a task also considered to assess processing speed [41], was not significantly impaired in the WMZ when sleep deprived, though the magnitude of the difference meets criteria for a small effect size ($d$ = 0.34). This difference may be attributable to the tasks themselves: The performance outcome on the IDN is RT, a direct measure of processing speed, while performance on the DSST is the number of correct responses made within the task's 2-min time limit. While a reduced number of correct responses on the DSST may reflect participants responding more slowly and seeing fewer trials during sleep deprivation, this highlights the importance of considering task design when comparing results across and within studies.

Our findings are also consistent with the meta-analysis by Lim and Dinges [2]. They reported that sleep deprivation resulted in the greatest impairment on simple RT measures, with large effect sizes (mean Hedges' $g$ = –0.76 and –0.73 for lapses and RT, respectively), while speed and accuracy were also impaired on tasks of greater complexity, with medium effect sizes (mean Hedges' $g$ ranging between –0.31 and –0.55). Morning performance on individual tests in this study followed this pattern: PVT performance and vigilant attention (DET) were most adversely impacted by sleep deprivation, with large effect sizes, while measures of complex attention/information processing and recognition memory deteriorated to a lesser extent, with medium effect sizes. In the WMZ, however, performance was undiminished on these measures and the accuracy composite score, while the PVT, vigilant attention, and the RT composite remained strongly impaired. These findings expand on those of the meta-analysis by highlighting the importance of considering the circadian timing of tests when measuring cognitive function during sleep deprivation. While it is hypothesized that cognitive improvement during the WMZ is due to an increased circadian drive for alertness to counter the rising pressure to sleep due to extended time awake [5, 58], this is inconsistent with the finding that, in the WMZ during sleep deprivation, accuracy is maintained, but response speed is not. This may indicate that the impact of the WMZ is test specific, and potentially goes beyond simply promoting alertness (see below).

Our finding that tests of complex attention and working memory were vulnerable to sleep deprivation during the morning hours, but not during the WMZ, contrasts with previous

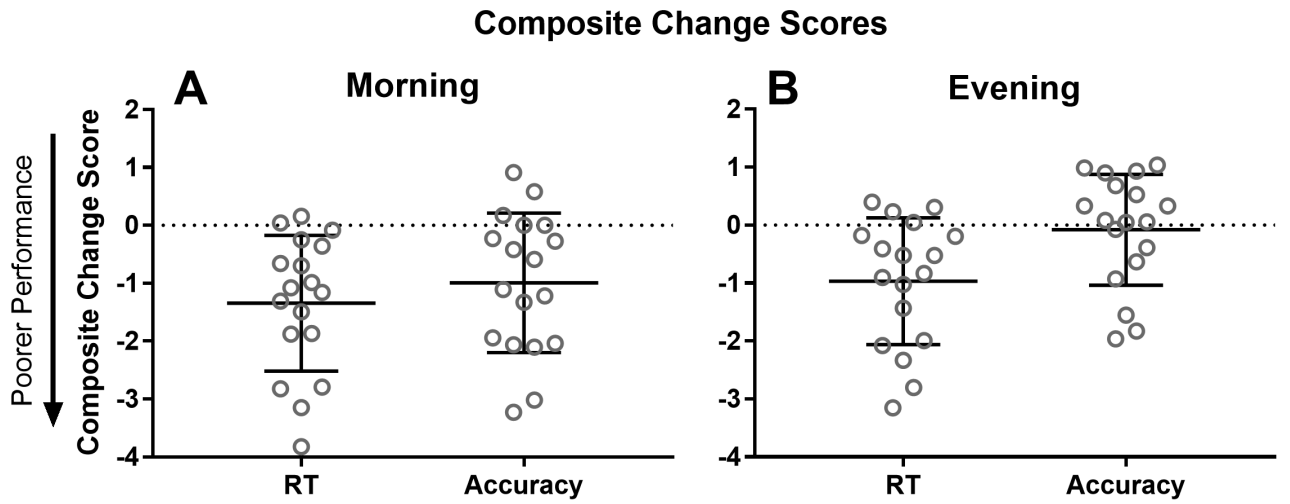


**Figure 4.** Composite scores for the change from well-rested performance during sleep deprivation. The composite score represents a z-score (derived from a normative sample), averaged across the two tasks that make up RT (attention tasks) and Accuracy (memory tasks). The arrow direction indicates poorer performance during sleep deprivation. (A) Composite change scores on Cogstate tests between well-rested (3 hours awake) and sleep deprived (27 hours awake) performance in the morning; (B) Composite change scores on Cogstate tests between well-rested (13 hours awake) and sleep deprived (37 hours awake) performance in the evening. Black lines with error bars represent the means and *SD*s; circles represent individual performance. The dotted line at zero on the y-axis indicates no change in performance between well-rested and sleep-deprived performance.

results. In other studies, verbal memory, working memory, and complex attention were impaired during the evening following 34–36 hours of sleep deprivation [18, 24, 25, 28]. While this discrepancy may be due to task characteristics (i.e. our tasks were of shorter duration, which is known to be less sensitive to the effects of sleep deprivation [59]), it is also possible that participants in previous studies were not tested in their WMZ, as the tests were scheduled relative to habitual wake time without a measure of circadian timing (WMZ). Our data highlight the need to better understand the potential task-dependent improvement in performance during the WMZ. Future studies may assess this with longer duration tasks, commonly used within the sleep field. Another consideration for our finding is that there may be a compensatory response in the WMZ that overcomes deficits only on particular tasks, or only for brief periods of time.

While compensatory responses are evident during sleep deprivation [23, 24, 60], they are affected by cognitive domain, task complexity [14, 15], and time on task [61, 62]. For example, tasks requiring long bouts of attention (>30 minutes) are associated with decreased thalamic activation [62], while tasks requiring short bouts of attention show enhanced thalamic activation on functional magnetic resonance imaging (fMRI) [61]. While the extent to which compensatory responses are modulated by time of day remains unknown, our results may reflect the capacity to maintain performance due to a compensatory cerebral response unique to the WMZ. This speculation is supported by our previous work where, following 35 hours of sleep deprivation, there was no behavioral change in recognition memory on a short (360 s) task of verbal learning, yet compensatory responses, as indicated by increased frontal activation and additional recruitment from parietal areas, were observed [24]. We therefore pose an intriguing question as to whether the WMZ is more than simply an increased drive for alertness, but instead represents a biologically unique point in time that initiates a compensatory response to maintain cognitive function. This speculation echoes a recent novel finding describing changes in cortical excitability during the WMZ [63]. Cortical excitability reflects the equilibrium between excitatory and inhibitory neurons that allow for optimal cognitive function to occur. Increased excitability is associated with disease states (e.g. epilepsy, dementia, Attention Deficit Hyperactivity Disorder [ADHD]) and cognitive dysfunction [64]. Ly and colleagues showed that cortical excitability increased across the waking day but returned to a baseline value during the WMZ. Such was the strength of the association between cortical excitability, circadian phase and performance, the authors argued that cortical excitability represented a circadian mechanism by which performance was maintained at the end of the normal waking day. By this argument, the WMZ is more than simply a state of heightened alertness, but instead a time where cognitive systems are mostly intact, which is consistent with our findings. This hypothesis may also explain the plethora of studies showing cerebral compensatory responses on fMRI during the evening [14, 15, 20, 23, 24, 60]. The extent to which cortical excitability may become more stable in the WMZ during sleep deprivation, and the relationship that may have with fMRI signals, is however unknown.

Our study has a number of limitations and our results should be interpreted with these caveats. First, we tested a relatively small sample of healthy young adults, and thus our results may not be reflective of older adults, shift workers, or individuals with sleep disorders. Further research is needed to assess the generalizability of these results to clinical populations and operational contexts. Second, due to the small sample size we may have been underpowered to detect an effect during the WMZ. While our sample size is comparable to other studies utilizing this design and study outcomes [5, 8, 65, 66], we corrected for multiple comparisons using a FDR, a less conservative method of correction, to reduce the potential for a type 1 error, plus we report effect sizes to support our findings: At 27 hours awake, we found moderate to large effect sizes for all outcomes, which indicates analyses were adequately powered, whereas for 37 hours awake effect sizes were large for vigilant attention outcomes, but small for other cognitive tests. A second possible limitation, inherent in study designs of this nature, was that our cognitive battery was always administered in the same order,

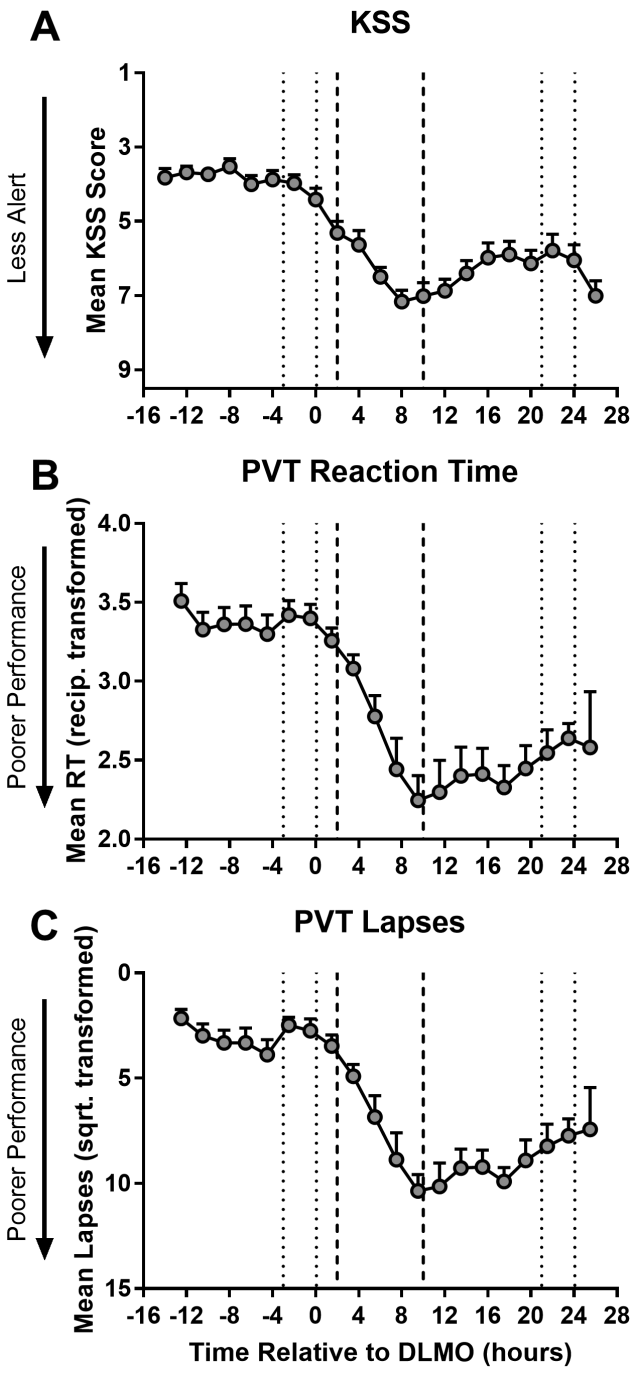


**Figure 5.** Psychomotor Vigilance Task (PVT) performance and KSS scores at each time point relative to circadian phase during the constant routine. (A) Mean KSS scores; (B) Reciprocally transformed mean PVT reaction time (RT); (C) Mean number of square-root transformed PVT lapses. Symbols are the mean and error bars are standard error of the means. Data are plotted in 2-hour bins relative to DLMO (0) on the first evening. Dashed lines show the average timing of the sleep period relative to DLMO. Dotted lines show the average timing of the WMZ relative to DLMO.

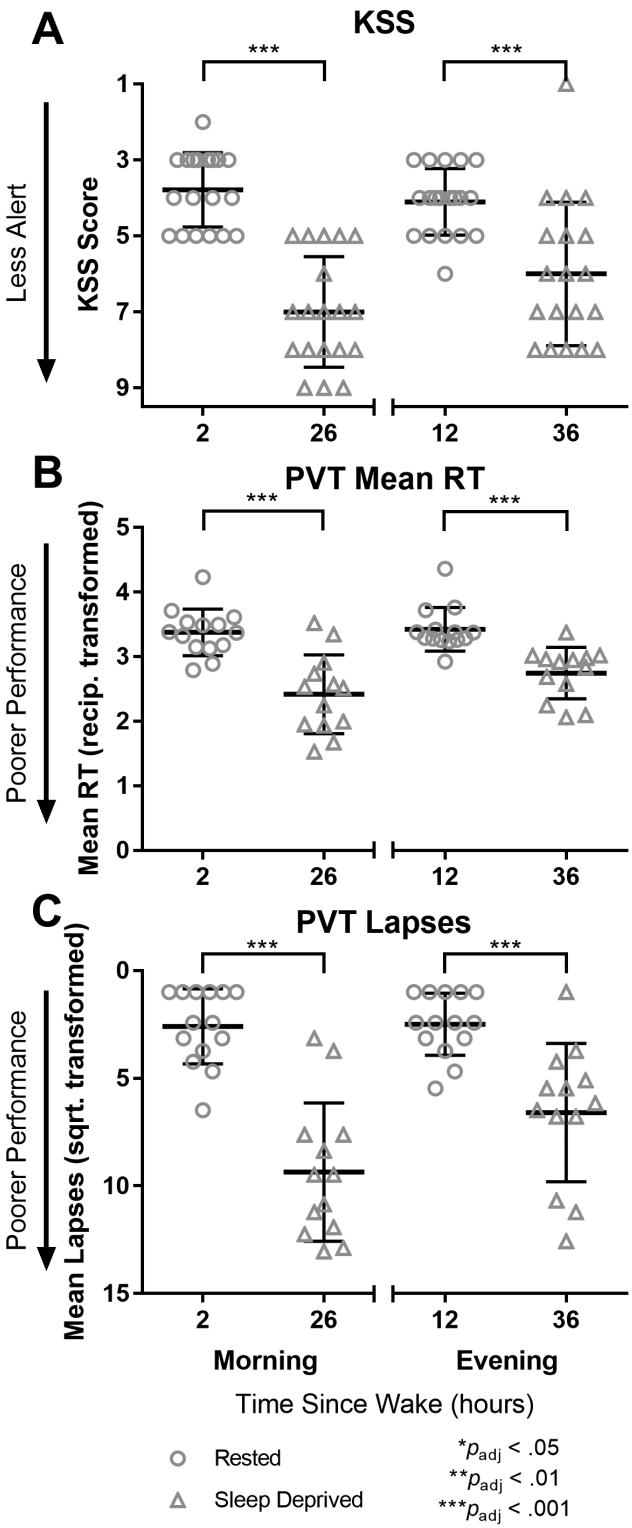


**Figure 6.** Comparison between well-rested and sleep-deprived PVT performance at the same time of day. (A) Mean KSS scores; (B) Reciprocally transformed mean PVT RT; (C) Mean number of square-root transformed PVT lapses. Black lines with error bars represent the means and SDs. Symbols are individual performance. Morning tests are grouped on the left of each plot; evening tests are grouped on the right.

and participants practiced the tasks only once before completing the tests during the CR. Previous research does not suggest there would be a strong learning effect with these tasks: In a sample of healthy young adults (comparable to our participants), no change was reported between a first and second administration of the tasks [67], while studies of healthy older adults and clinical populations reported only mild improvement between the first and second administrations of the test battery, and stability in performance thereafter [33, 34, 68]. Our data (Figure 3)

clearly shows the stability of performance between the second and third administrations of the task, at 3 hours and 13 hours (the first administration was on the first baseline day; Figure 1). Further, a learning effect would result in poorer performance at 3 hours, which would mask our reported finding that performance is impaired at 27 hours (fourth administration) relative to 3 hours (second administration). Based on our data and that of others we believe the single scheduled practice in our design was adequate to remove any learning effects from our data.

The results of this study have several implications. First, given that we report time-specific changes in cognitive function during sleep deprivation, we suggest that a measure of circadian phase is necessary to appropriately interpret the impact of sleep deprivation on cognitive performance, especially if tests are scheduled in the evening. Healthy participants show a ~5-hour range in circadian phase after maintaining stable 8-hour sleep patterns for multiple weeks [69, 70], while groups with more disrupted sleep patterns show even greater variability: for example, 7 hours in insomnia patients [71] and 12 hours in shift workers [72, 73]. Given the large majority of sleep and circadian studies schedule tests according to time since wake, differences in circadian phase of this magnitude could result in substantial variation in the circadian timing of cognitive assessment between participants. Second, we minimized the impact of task design on performance by using a battery comprising tasks that have comparable features, including task duration and visual presentation. Using tasks with similar features to assess different cognitive domains would enhance the comparability between studies, and may reduce the variance between studies reported as a limitation in meta-analytic approaches [2]. Third, the finding that performance on more complex cognitive tasks, particularly those assessing accuracy, is relatively preserved in the WMZ may be beneficial to shift working populations, such that tasks requiring accuracy might be best scheduled to occur during the WMZ during work schedules where sleep loss is inevitable. Finally, we found evidence of inter-individual variation in both circadian phase and cognitive performance. As we provide evidence for task-dependent and time-dependent effects in cognitive failure during sleep deprivation, identifying individuals at risk of cognitive failure, and the time at which they are most at risk, would represent a significant improvement in operational risk management where sleep loss remains common. Developing simplified methods of circadian phase to identify both periods of impairment and preserved cognitive function could therefore facilitate smart scheduling systems designed to maximize safety and productivity in the modern 24/7 workplace.

## Supplementary material

Supplementary material is available at *SLEEP* online.

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All authors have made substantial contributions to the work presented and have approved the final version of the manuscript. C.A. and S.F. designed the study with input from S.P.A.D., P.M., S.W.L., and S.M.W.R.; W.R.M. and S.F. were responsible for the collection of data; W.R.M. and S.F. analyzed the data; W.R.M., S.F., P.M., S.P.A.D., and C.A. interpreted the data and W.R.M. wrote the manuscript. All authors approved the final manuscript. We thank the study participants, technicians, staff, and students of the Monash University Sleep and Circadian Medicine Laboratory who aided data collection. We also thank Leilah Grant and Jinny Collet for research assistance in the study; Caroline Beatty for recruitment efforts; study physicians Dr. Simon Joosten and Dr. Eric Kuo; Sylvia Nguyen for conducting psychiatric screening; and Kellie Hamill for logistical help. We also gratefully acknowledge the assistance of the Adelaide Research Assay Facility for providing plasma melatonin analysis.

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## Ethical Approval

The study was approved by Monash University Human Research Ethics Committee.

*Conflict of interest statement*. The authors report no conflicts of interests related to the results reported in this paper, but in the interest of full disclosure: W.R.M. received a top-up Scholarship from the Cooperative Research Centre for Alertness, Safety and Productivity, and S.F. served as a Project Leader. S.P.A.D. has no conflicts of interests related to the research or results reported in this paper. P.M. is a full-time employee of Cogstate, the company that supplied some of the cognitive assessments for this study. S.W.L. has no conflicts of interests related to the research or results reported in this paper. In the interests of full disclosure, commercial interests from the last 3 years (2014–2017) are listed below. S.W.L. has received consulting fees from the Atlanta Falcons, Atlanta Hawks, Carbon Limiting Technologies Ltd on behalf of PhotoStar LED, Perceptive Advisors, Serrado Capital, Slingshot Insights; and has current consulting contracts with Akili Interactive, Consumer Sleep Solutions, Delos Living LLC, Headwaters Inc., Hintsa Performance AG, Light Cognitive, Mental Workout, Pegasus Capital Advisors LP, PlanLED, OpTerra Energy Services Inc., Wyle Integrated Science and Engineering. SWL has received unrestricted equipment gifts from Biological Illuminations LLC, Bionetics Corporation and F.LUX Software LLC; has equity in iSLEEP, Pty; advance author payment and/or royalties from Oxford University Press; honoraria plus travel, accommodation and/or meals for invited seminars, conference presentations or teaching from BHP Billiton, Estee Lauder, Lightfair, Informa Exhibitions (USGBC), Teague; travel, accommodation and/or meals only (no honoraria) for invited seminars, conference presentations or teaching from FASEB, Hintsa Performance AG, Lightfair, and USGBC. S.W.L. has completed investigator-initiated research grants from Biological Illumination LLC and Vanda Pharmaceuticals Inc and has an ongoing investigator-initiated grant from F. Lux Software LLC; completed service agreements from Rio Tinto Iron Ore and Vanda Pharmaceuticals Inc.; and completed three sponsor-initiated clinical research contracts from Vanda Pharmaceuticals Inc. S.W.L. holds a process patent for "Systems and methods for determining and/or controlling sleep quality," which is assigned to the Brigham and Women's Hospital per Hospital policy. S.W.L. has also served as a paid expert on behalf of several public bodies on arbitrations related to sleep, light, circadian rhythms and/or work hours for City of Brantford, Canada, and legal proceedings related to light,

sleep and health. S.W.L. is also a Program Leader for the CRC for Alertness, Safety and Productivity, Australia. S.M.W.R. reports that he has served as a consultant through his institution to Vanda Pharmaceuticals, Philips Respironics, EdanSafe, The Australian Workers' Union, National Transport Commission, Transport Accident Commission, New South Wales Department of Education and Communities, and has through his institution received research grants and/or unrestricted educational grants from Vanda Pharmaceuticals, Shell, Teva Pharmaceuticals, Rio Tinto, Seeing Machines, Takeda Pharmaceuticals North America, Philips Lighting, Philips Respironics, Cephalon, and ResMed Foundation, and reimbursements for conference travel expenses from Vanda Pharmaceuticals. His institution has received equipment donations or other support from Optalert, Compumedics, and Tyco Healthcare. He has served as an expert witness and/or consultant to shift work organizations. S.M.W.R. also serves as a Program Leader in the Cooperative Research Centre for Alertness, Safety and Productivity. C.A. has received a research award/prize from Sanofi-Aventis; contract research support from VicRoads, Rio Tinto Coal Australia, National Transport Commission, Tontine/Pacific Brands; and lecturing fees from Brown Medical School/Rhode Island Hospital, Ausmed, Healthmed and TEVA Pharmaceuticals; and reimbursements for conference travel expenses from Philips Healthcare. In addition, she has served as a consultant through her institution to the Rail, Bus and Tram Union, the Transport Accident Commission (TAC) and the National Transportation Committee (NTC). She has also served as an expert witness and/or consultant in relation to fatigue and drowsy driving. C.A. is a Theme Leader in the Cooperative Research Centre for Alertness, Safety and Productivity.

## References


1. Rajaratnam SM, *et al*. Health in a 24-h society. *Lancet*. 2001;**358**(9286):999–1005.
2. Lim J, *et al*. A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychol Bull*. 2010;**136**(3):375–389.
3. Dawson D, *et al*. Fatigue, alcohol and performance impairment. *Nature*. 1997;**388**(6639):235.
4. Doran SM, *et al*. Sustained attention performance during sleep deprivation: evidence of state instability. *Arch Ital Biol*. 2001;**139**(3):253–267.
5. Dijk DJ, *et al*. Circadian and sleep/wake dependent aspects of subjective alertness and cognitive performance. *J Sleep Res*. 1992;**1**(2):112–117.
6. Wyatt JK, *et al*. Circadian temperature and melatonin rhythms, sleep, and neurobehavioral function in humans living on a 20-h day. *Am J Physiol Regul Integr Comp Physiol*. 1999;**277**(4):R1152–R1163.
7. Zhou X, *et al*. Sleep, wake and phase dependent changes in neurobehavioral function under forced desynchrony. *Sleep*. 2011;**34**(7):931–941.
8. Burke TM, *et al*. Sleep inertia, sleep homeostatic and circadian influences on higher-order cognitive functions. *J Sleep Res*. 2015;**24**(4):364–371.
9. Shekleton JA, *et al*. Improved neurobehavioral performance during the wake maintenance zone. *J Clin Sleep Med*. 2013;**9**(4):353–362.
10. Strogatz SH, *et al*. Circadian pacemaker interferes with sleep onset at specific times each day: role in insomnia. *Am J Physiol*. 1987;**253**(1 Pt 2):R172–R178.
11. Lavie P. Ultrashort sleep-waking schedule. III. 'Gates' and 'forbidden zones' for sleep. *Electroencephalogr Clin Neurophysiol*. 1986;**63**(5):414–425.
12. Lo JC, *et al*. Effects of partial and acute total sleep deprivation on performance across cognitive domains, individuals and circadian phase. *PLoS One*. 2012;**7**(9):e45987.
13. Chellappa SL, *et al*. Daily circadian misalignment impairs human cognitive performance task-dependently. *Sci Rep*. 2018;**8**(1):3041.
14. Drummond SP, *et al*. Increasing task difficulty facilitates the cerebral compensatory response to total sleep deprivation. *Sleep*. 2004;**27**(3):445–451.
15. Drummond SP, *et al*. Compensatory recruitment after sleep deprivation and the relationship with performance. *Psychiatry Res*. 2005;**140**(3):211–223.
16. Chee MW, *et al*. Sleep deprivation and its effects on object-selective attention. *Neuroimage*. 2010;**49**(2):1903–1910.
17. Chee MW, *et al*. Lapsing when sleep deprived: neural activation characteristics of resistant and vulnerable individuals. *Neuroimage*. 2010;**51**(2):835–843.
18. Drummond SP, *et al*. Effects of two nights sleep deprivation and two nights recovery sleep on response inhibition. *J Sleep Res*. 2006;**15**(3):261–265.
19. Alhola P, *et al*. Sleep deprivation, cognitive performance, and hormone therapy in postmenopausal women. *Menopause*. 2005;**12**(2):149–155.
20. Chee MW, *et al*. Functional imaging of working memory after 24 hr of total sleep deprivation. *J Neurosci*. 2004;**24**(19):4560–4567.
21. Choo WC, *et al*. Dissociation of cortical regions modulated by both working memory load and sleep deprivation and by sleep deprivation alone. *Neuroimage*. 2005;**25**(2):579–587.
22. Chuah YM, *et al*. The neural basis of interindividual variability in inhibitory efficiency after sleep deprivation. *J Neurosci*. 2006;**26**(27):7156–7162.
23. Drummond SP, *et al*. Increased cerebral response during a divided attention task following sleep deprivation. *J Sleep Res*. 2001;**10**(2):85–92.
24. Drummond SP, *et al*. Altered brain response to verbal learning following sleep deprivation. *Nature*. 2000;**403**(6770):655–657.
25. Chee MW, *et al*. Functional imaging of working memory following normal sleep and after 24 and 35 h of sleep deprivation: correlations of fronto-parietal activation with performance. *Neuroimage*. 2006;**31**(1):419–428.
26. Anderson C, *et al*. Bargaining and trust: the effects of 36-h total sleep deprivation on socially interactive decisions. *J Sleep Res*. 2010;**19**(1 Pt 1):54–63.
27. McCarthy ME, *et al*. Decreased attentional responsivity during sleep deprivation: orienting response latency, amplitude, and habituation. *Sleep*. 1997;**20**(2):115–123.
28. Mander BA, *et al*. Sleep deprivation alters functioning within the neural network underlying the covert orienting of attention. *Brain Res*. 2008;**1217**:148–156.
29. Anderson C, *et al*. Sleep deprivation lowers inhibition and enhances impulsivity to negative stimuli. *Behav Brain Res*. 2011;**217**(2):463–466.
30. Lee HJ, *et al*. Cognitive deterioration and changes of P300 during total sleep deprivation. *Psychiatry Clin Neurosci*. 2003;**57**(5):490–496.
31. Duffy JF, *et al*. Getting through to circadian oscillators: why use constant routines? *J Biol Rhythms*. 2002;**17**(1):4–13.
32. National Health and Medical Research Council. *Australian Dietary Guidelines*. Canberra, Australia: National Health and Medical Research Council; 2013.

33. Fredrickson J, *et al*. Evaluation of the usability of a brief computerized cognitive screening test in older people for epidemiological studies. *Neuroepidemiology*. 2010;**34**(2):65–75.
34. Hammers D, *et al*. Reliability of repeated cognitive assessment of dementia using a brief computerized battery. *Am J Alzheimers Dis Other Demen*. 2011;**26**(4):326–333.
35. Lim YY, *et al*. Three-month stability of the CogState brief battery in healthy older adults, mild cognitive impairment, and Alzheimer's disease: results from the Australian Imaging, Biomarkers, and Lifestyle-rate of change substudy (AIBL-ROCS). *Arch Clin Neuropsychol*. 2013;**28**(4):320–330.
36. Darby D, *et al*. Community screening for early signs of dementia. *Alzheimers Dement*. 2009;**5**:e3–e4.
37. Cho W, *et al*. Additive effects of a cholinesterase inhibitor and a histamine inverse agonist on scopolamine deficits in humans. *Psychopharmacology (Berl)*. 2011;**218**(3):513–524.
38. Maruff P, *et al*. A statistical approach for classifying change in cognitive function in individuals following pharmacologic challenge: an example with alprazolam. *Psychopharmacology (Berl)*. 2006;**186**(1):7–17.
39. Falleti MG, *et al*. Qualitative similarities in cognitive impairment associated with 24 h of sustained wakefulness and a blood alcohol concentration of 0.05%. *J Sleep Res*. 2003;**12**(4):265–274.
40. Darby DG, *et al*. Intraindividual cognitive decline using a brief computerized cognitive screening test. *Alzheimers Dement*. 2012;**8**(2):95–104.
41. Maruff P, *et al*. Validity of the CogState brief battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. *Arch Clin Neuropsychol*. 2009;**24**(2):165–178.
42. Maruff P, *et al*.; AIBL Research Group. Clinical utility of the Cogstate brief battery in identifying cognitive impairment in mild cognitive impairment and Alzheimer's disease. *BMC Psychol*. 2013;**1**(1):30.
43. Luce RD. *Response Times: Their Role in Inferring Elementary Mental Organization*. New York, NY: Oxford University Press; 1986.
44. Akerstedt T, *et al*. Subjective and objective sleepiness in the active individual. *Int J Neurosci*. 1990;**52**(1-2):29–37.
45. Reyner LA, *et al*. Falling asleep whilst driving: are drivers aware of prior sleepiness? *Int J Legal Med*. 1998;**111**(3):120–123.
46. Lewy AJ, *et al*. The dim light melatonin onset as a marker for circadian phase position. *Chronobiol Int*. 1989;**6**(1):93–102.
47. Kennaway DJ, *et al*. Circadian rhythm of free melatonin in human plasma. *J Clin Endocrinol Metab*. 1998;**83**(3):1013–1015.
48. Voultsios A, *et al*. Salivary melatonin as a circadian phase marker: validation and comparison to plasma melatonin. *J Biol Rhythms*. 1997;**12**(5):457–466.
49. Benloucif S, *et al*. Measuring melatonin in humans. *J Clin Sleep Med*. 2008;**4**(1):66–69.
50. Dinges DF, *et al*. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. *Sleep*. 1997;**20**(4):267–277.
51. Maruff P, *et al*. Cognitive deterioration associated with an expedition in an extreme desert environment. *Br J Sports Med*. 2006;**40**(6):556–560.
52. Bland JM, *et al*. Measurement error. *BMJ*. 1996;**313**(7059):744.
53. Schwarz G. Estimating the dimension of a model. *Ann Stat*. 1978;**6**(2):461–464.
54. Benjamini Y, *et al*. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol*. 1995;**57**(1):289–300.
55. Verhoeven KJ, *et al*. Implementing false discovery rate control: increasing your power. *Oikos*. 2005;**108**(3):643–647.
56. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Lawrence Earlbaum; 1988.
57. Shekleton JA, *et al*. Searching for the daytime impairments of primary insomnia. *Sleep Med Rev*. 2010;**14**(1):47–60.
58. Dijk DJ, *et al*. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *J Neurosci*. 1995;**15**(5 Pt 1):3526–3538.
59. Caldwell JA, *et al*. Effects of task duration on sensitivity to sleep deprivation using the multi-attribute task battery. *Behav Res Methods Instrum Comput*. 1998;**30**(4):651–660.
60. Drummond SP, *et al*. The effects of total sleep deprivation on cerebral responses to cognitive performance. *Neuropsychopharmacology*. 2001;**25**(5 Suppl):S68–S73.
61. Portas CM, *et al*. A specific role for the thalamus in mediating the interaction of attention and arousal in humans. *J Neurosci*. 1998;**18**(21):8979–8989.
62. Thomas M, *et al*. Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *J Sleep Res*. 2000;**9**(4):335–352.
63. Ly JQ, *et al*. Circadian regulation of human cortical excitability. *Nat Commun*. 2016;**7**:11828.
64. Bolden LB, *et al*. Cortical excitability and neuropsychological functioning in healthy adults. *Neuropsychologia*. 2017;**102**:190–196.
65. St Hilaire MA, *et al*. Classifying performance impairment in response to sleep loss using pattern recognition algorithms on single session testing. *Accid Anal Prev*. 2013;**50**:992–1002.
66. Chua EC, *et al*. Sustained attention performance during sleep deprivation associates with instability in behavior and physiologic measures at baseline. *Sleep*. 2014;**37**(1):27–39.
67. Louey AG, *et al*. Detecting cognitive impairment after concussion: sensitivity of change from baseline and normative data methods using the CogSport/Axon cognitive test battery. *Arch Clin Neuropsychol*. 2014;**29**(5):432–441.
68. Lees J, *et al*. Calibration and cross-validation of MCCB and CogState in schizophrenia. *Psychopharmacology (Berl)*. 2015;**232**(21-22):3873–3882.
69. Sletten TL, *et al*. Timing of sleep and its relationship with the endogenous melatonin rhythm. *Front Neurol*. 2010;**1**:137.
70. Wright KP Jr, *et al*. Intrinsic period and light intensity determine the phase relationship between melatonin and sleep in humans. *J Biol Rhythms*. 2005;**20**(2):168–177.
71. Flynn-Evans EE, *et al*. Circadian phase and phase angle disorders in primary insomnia. *Sleep*. 2017;**40**(12).
72. Ftouni S, *et al*. Ocular measures of sleepiness are increased in night shift workers undergoing a simulated night shift near the peak time of the 6-sulfatoxymelatonin rhythm. *J Clin Sleep Med*. 2015;**11**(10):1131–1141.
73. Dumont M, *et al*. Profile of 24-h light exposure and circadian phase of melatonin secretion in night workers. *J Biol Rhythms*. 2001;**16**(5):502–511.