

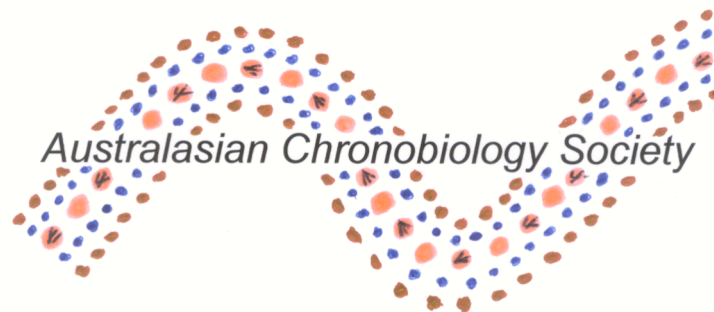
Living in a 24/7 World:

The impact of circadian disruption on sleep, work and health

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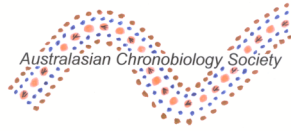
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Chapter 4

Sleep, wake and phase dependent changes in subjective alertness

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Aims: To systematically examine the impact of prior wake, sleep dose and circadian phase on subjective alertness.

Methods: Twenty-seven young males participated in one of two 12-day 28h forced desynchrony protocols varying in sleep dose (9.3h vs. 4.7h), where subjective alertness was assessed at various combinations of prior wake and circadian phase. Subjective alertness was measured using a visual analogue scale. Circadian phase was estimated using core body temperature.

Results: A mixed-effects regression analysis with prior wake, circadian phase and sleep dose as fixed terms and participant as a random term revealed a sleep dose x prior wake x circadian phase interaction.

Discussion: The sleep dose x prior wake x circadian phase interaction indicates that the adverse impact of sleep restriction on subjective alertness is prominent at early waking hours, particularly during the biological night.

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Introduction

Staying alert is essential for daily activities. Our understanding of how alertness is regulated is not yet complete, though we do know, from our day-to-day experience, that how alert we feel is closely related to our sleep-wake schedules. In fact, the scientific understanding of how alertness is regulated is built on sleep-wake regulation, which is widely believed to be underpinned by interactions between two processes.¹ A homeostatic process operates to balance the duration of wakefulness with the duration of sleep through an exponential saturating increase in a pressure for sleep over time awake and an exponential dissipation in this pressure over time asleep. A circadian process operates to keep track of internal biological time or circadian

phase through the promotion of wakefulness during the biological day and the promotion of sleep during the biological night.

From total sleep deprivation (TSD) studies⁵ we know that subjective alertness declines as homeostatic sleep pressure increases over time awake, and that at the same time, subjective alertness also fluctuates over circadian phase with a peak during the biological day and a trough during the biological night. From partial sleep deprivation (PSD) studies⁵ we know that subjective alertness is reduced by sleep restriction (<7h) of a single night and of multiple successive nights because of incomplete dissipations of sleep pressure. However, in both TSD and PSD studies, the homeostatic and circadian processes are

synchronized so that the phase relationship between prior wake and circadian phase is fixed. As such, subjective alertness was assessed at limited combinations of prior wake and circadian phase. Consequently, the interactive influences of the two processes are not quantified.

The limitation of TSD and PSD studies is overcome in forced desynchrony (FD) studies,⁹ where the period of sleep-wake cycle is either extended (e.g., 28h) or shortened (e.g., 20h) beyond the normal entrainment of the circadian system.³ The imposed sleep-wake cycle forces a desynchrony between the homeostatic and circadian processes such that subjective alertness was assessed at various combinations of circadian phase and prior wake, allowing quantifications of the homeostatic-circadian interactions. From FD studies we know that the two processes interact in a non-linear fashion such that the circadian influence on subjective alertness becomes more prominent as homeostatic sleep pressure increases.⁹ FD studies are limited in holding the sleep dose constant at a habitual level, such that the homeostatic-circadian interactions are solely depicted in terms of prior wake and circadian phase. Consequently, the interactions between the two processes based on all three factors – prior wake, circadian phase and sleep dose – remain unknown.

To overcome the limitation of FD studies, we designed a novel protocol – a sleep restricted forced desynchrony protocol – in which the sleep dose is reduced below a habitual level while the homeostatic and circadian processes are in a state of forced desynchrony. As such, subjective alertness is assessed at various combinations of prior wake and circadian phase when sleep is restricted. We compare data from this protocol to those from a standard FD protocol where subjective alertness is assessed at various combinations of prior wake and circadian phase when sleep dose is not

intentionally restricted. This comparison allows us to reveal the interaction between homeostatic and circadian processes on subjective alertness in terms of all three factors – prior wake, sleep dose and circadian phase.

Methods

Participants

Twenty-seven young males (age, $M = 22.1$, $SD = 3.1$ yrs) gave written consent to participate in the study. Based on the responses to a general health questionnaire, the participants did not have any medical conditions, psychiatric or sleep disorders; none of the participants were taking any prescribed medication or had a high consumption of alcohol or caffeine at the time of the study. The participants were not shift workers and/or had not recently undertaken transmeridian travel. Participants' self-report habitual sleep-wake patterns were similar, with a mean bedtime at 23:12h, a mean get-up time at 08:15h and a mean sleep duration of 8.1h.

Measures

Subjective alertness was assessed using a Visual Analogue Scale (VAS),⁶ which requires participants to mark on a 100cm line with 'struggling to remain awake' and 'extremely alert and wide awake' at either end. Core body temperature was sampled at 1-min intervals throughout the study using rectal thermistors (Cincinnati Sub-Zero Products, Cincinnati, OH). Sleep was assessed using polysomnography (Compumedics E-Series EEG/PSG system, Melbourne, Australia). PSG recordings included C3/A2 and C4/A1 electroencephalogram, electrooculogram and electromyogram.

Protocol

The current study employed a between-participant design where participants participated in one of two 12-calendar-day 28h forced desynchrony protocols varying in sleep dose. A standard FD protocol ($n = 13$; age 22.5 ± 2.2 yrs; body mass index 22.2 ± 2.2 kg/m²) comprised 7

x 28h sleep/wake cycle with a sleep dose of 9.3h/cycle (~ 8h in bed/24h). A sleep restricted FD protocol ($n = 14$; age 21.8 ± 3.8 yrs; body mass index 22.4 ± 2.3 kg/m²) comprised 7 x 28h sleep/wake cycle with a sleep dose of 4.7h/cycle (~ 4h in bed/24h). Prior to the FD phase (i.e., 7 x 28h sleep/wake cycle), both protocols included two training periods a baseline period. During the training periods, VAS alert was first introduced to the participants. During the baseline period, subjective alertness was assessed five times at a 2h interval from 10:00h to establish each individual's baseline alertness level. During the FD phase, subjective alertness was assessed every 2.5h, from 2h into each scheduled wake period. In participants' 'free' time, only non-strenuous activities (e.g., reading books) were permitted, and no naps were allowed. Participants had minimal interaction with each other. To ensure compliance, participants were closely monitored by researchers either in person or via a closed circuit television system.

All experiments were carried out in a sound attenuated sleep laboratory, which was maintained as a temporally isolated environment. Maximal ambient light intensity during wake periods was 10-15 lux at head height and less than 0.03 lux during sleep periods. Throughout the study, the target ambient temperature was $22 (\pm 1)^\circ\text{C}$. Both protocols conformed to the guidelines established by the National Health and Medical Research Council, and were approved by the Human Research Ethics Committee at the University of South Australia.

Data analyses

PSG recordings were manually scored in 30s epochs using the established criteria.⁷ Circadian phases of each participant were estimated using core body temperature.⁴ Circadian phases were divided into 6 x 60° bins with midpoints at 0° (i.e., core body temperature minimum), 60°, 120°, 180°, 240° and 300°. Each individual's VAS scores during the FD days were

expressed relative to his own baseline VAS score (i.e., the average of five baseline VAS scores) to control for between-participant variations in alertness level. A higher VAS score indicates a more alert state. The standardized values were then assigned to one of two sleep dose conditions (i.e., 9.33h & 4.76h), one of nine prior wake (i.e., 2h, 4.5h, 7h, 9.5h, 14.5h, 17h, 19.5h & 22h) and one of six circadian phase bins. Data were analyzed using a mixed-effects regression model, with SLEEP DOSE, CIRCADIAN PHASE and PRIOR WAKE as fixed terms, and 'PARTICIPANT' ($N = 27$) as a random term. We first tested all main effects and all possible two-way interactions, and then removed all non-significant two-way interactions from further analysis.

Results

The participants in the two protocols were not different in age, body mass index, self-report habitual bed time, get-up time and sleep duration. During the study, participants in the standard protocol obtained an average of 7.71h sleep (± 0.65 h); participants in the sleep restricted protocol obtained an average of 4.49h sleep (± 0.09 h).

There was a main effect of CIRCADIAN PHASE ($F_{5,1471} = 3.2$, $p=0.007$), with participants feeling least alert at the circadian nadir, and feeling most alert at circadian phases 180° to 240° (i.e., day time under entrainment) (Figure 1A). There was a main effect of PRIOR WAKE ($F_{1,1471} = 412.4$, $p<0.001$), with participants feeling less alert over time awake (Figure 1B). There was a main effect of SLEEP DOSE ($F_{1,33} = 28.7$, $p<0.001$), with participants in the sleep restricted protocol feeling less alert than participants in the standard protocol (Figure 1).

There was a PRIOR WAKE x SLEEP DOSE interaction ($F_{1,1471} = 42.1$, $p<0.001$), such that the impact of SLEEP DOSE on subjective alertness became less

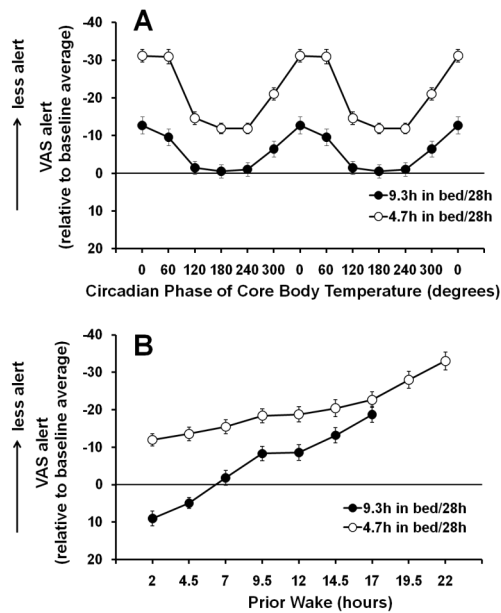


Fig.1 Subjective alertness (y-axis), as assessed using VAS alert, is plotted as a function of circadian phase (Panel A) and as a function of prior wake (Panel B) when sleep dose is 9.3h/28h and when sleep dose is 4.7h/28h. VAS alert values are expressed relative to baseline average. Y-axes are reversed such that a higher point indicates a less alert state. Horizontal lines indicate baseline subjective alertness level.

pronounced as prior wake increased (Figure 1B). There was a significant PRIOR WAKE x CIRCADIAN PHASE interaction ($F_{5,1471} = 6.58, p < 0.001$), such that the circadian waveform (i.e., effect of circadian phase) became more pronounced with increasing hours awake for both sleep dose conditions (Figure 2A & B). There was a significant PRIOR WAKE x CIRCADIAN PHASE x SLEEP DOSE interaction ($F_{5,1471} = 3.54, p = 0.004$). This three-way interaction was interpreted as changes in the impact of sleep dose on subjective alertness as a function of prior wake and circadian phase. To facilitate this interpretation, the extents of the impact of sleep dose, as visualized by the differences in the mean

VAS alert between the two sleep dose conditions, are plotted at different combinations of prior wake and circadian phase (Figure 2C). Color changes in this contour plot reflect changes in the extent of the impact of sleep dose: the warmer the color, the greater the adverse impact of sleep restriction. It is clear that the adverse impact of sleep restriction was prominent at early waking hours, particularly near the circadian nadir.

Discussion

The main effects of circadian phase and prior wake on subjective alertness are consistent with previous TSD and FD studies,^{5,9} and re-enforce our understanding on the two-process regulation of subjective alertness. Under homeostatic regulation, subjective alertness declined as homeostatic sleep pressure increased over time awake. Under circadian regulation, subjective alertness reached a peak during the biological day when wakefulness is promoted, and reached a trough during the biological night when sleep is promoted. Further, our PRIOR WAKE x CIRCADIAN PHASE interaction is consistent with previous FD studies,⁹ and confirms the non-linear interaction between the homeostatic and circadian processes, i.e., the circadian influence is enhanced as homeostatic sleep pressure increases.

The adverse impact of sleep restriction also agrees with previous PSD studies⁸ in that the sleep restriction impairs subjective alertness. Different from previous PSD studies though, our study

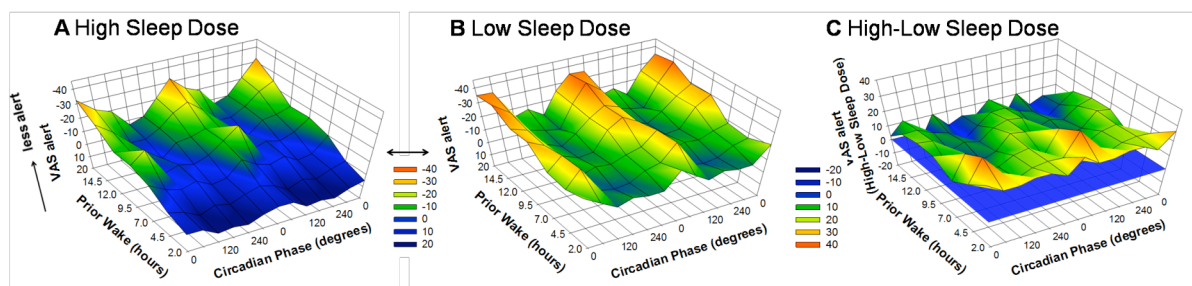


Fig.2 Subjective alertness (z-axis), as assessed using VAS alert, is plotted as a function of circadian phase (x-axis) and prior wake (y-axis) when sleep dose is 9.3h/28h (Panel A) and when sleep dose is 4.7h/28h (Panel B). VAS alert values are expressed relative to baseline average. Z-axes are reversed such that a higher point indicates a less alert state. Panel C presents the differences in mean VAS alert between the two sleep dose conditions (high-low sleep dose condition) as a function of prior wake and circadian phase. To highlight the extent of the impact of sleep dose, Panel C also includes a zero plain which indicates no differences in VAS alert between the two sleep dose conditions.

examined changes in the impact of sleep restriction as a function of prior wake and circadian phase. We found a SLEEP DOSE \times PRIOR WAKE interaction such that the impact of sleep restriction was reduced over time awake. If the difference in subjective alertness at early waking hours reflects the difference in sleep pressure due to sleep restriction, then the reducing differences between the sleep dose conditions over time awake would suggest that sleep pressure built up more quickly after a high sleep dose than after a low sleep dose. This result may reflect the exponential saturating build-up of sleep pressure over time awake—the speed of this build-up depends on the starting point on the curve.

We also found a SLEEP DOSE \times PRIOR WAKE \times CIRCADIAN PHASE interaction such that the prominent impact of sleep dose at early waking hours was particularly observed during the biological night. This result has important implications for predicting subjective alertness. It suggests that previous PSD studies where the impact of sleep restriction is only studied during the day may under-estimate the impact of sleep restriction experienced by individuals who work at night. Mathematical models that use prior wake, circadian phase and sleep dose to estimate alertness could be improved if they were to incorporate this interaction.

A limitation of the present study is that it does not distinguish the impact of acute and chronic sleep restriction, implying that the impact of sleep dose is due to a combination of i) the incompletely dissipated sleep pressure from the most recent sleep restricted period and ii) the accumulated sleep pressure from multiple sleep restricted periods. To discern the contributions of acute and chronic sleep restriction to subjective alertness, future studies may need to include at least two FD cycles (i.e., 12 \times 28h day) and use ‘FD cycle’ as a rough indicator of the impact of chronic sleep restriction.²

Acknowledgements

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